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Rheumatoid arthritis: previously untreated early disease

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ABSTRACT

INTRODUCTION: Rheumatoid arthritis is a chronic autoimmune disease, which most often presents as a symmetrical polyarthritis of the hands and feet. Pharmacological treatments include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) and other disease-modifying anti-rheumatoid drugs (DMARDs), which may be synthetic (either conventional [csDMARDs] or targeted [tsDMARDs]) or biological (bDMARDs). METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical questions: What are the effects of methotrexate in combination with other csDMARDs versus methotrexate monotherapy in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)? What are the effects of bDMARDs as monotherapy versus methotrexate or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)? What are the effects of bDMARDs in combination with methotrexate versus methotrexate monotherapy or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)? What are the effects of glucocorticoids in combination with methotrexate or with other csDMARDs versus methotrexate or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)? We searched: Medline, Embase, The Cochrane Library and other important databases up to December 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 2058 studies. Of the full articles evaluated, 10 systematic reviews, 22 RCTs, and one follow-up report were added at this update. We performed a GRADE evaluation for 18 PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for 22 comparisons based on information about the effectiveness and safety of bDMARDs (monotherapy or combined with csDMARDs), csDMARDs (monotherapy or combined with other csDMARDs), glucocorticoids combined with methotrexate or other csDMARDs, and methotrexate (monotherapy or combined with other csDMARDs), identifying interventions which were likely or unlikely to be beneficial.

QUESTIONS

INTERVENTIONS

METHOTREXATE IN COMBINATION WITH OTHER CSDMARDS VERSUS METHOTREXATE MONOTHERAPY IN DMARD-NAÏVE PEOPLE WITH RHEUMATOID ARTHRITIS

Unlikely to be beneficial

BDMARDS AS MONOTHERAPY VERSUS METHOTREXATE OR OTHER CSDMARDS IN DMARD-NAÏVE PEOPLE WITH RHEUMATOID ARTHRITIS

Unknown effectiveness

BDMARDS IN COMBINATION WITH METHOTREXATE VERSUS METHOTREXATE MONOTHERAPY OR OTHER CSDMARDS IN DMARD-NAÏVE PEOPLE WITH RHEUMATOID ARTHRITIS

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Key points

- Rheumatoid arthritis is a chronic autoimmune disease, which most often presents as a symmetrical polyarthritis of the hands and feet.

  Pharmacological treatments include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) and other disease-modifying anti-rheumatoid drugs (DMARDs), which may be synthetic (sDMARDs: either conventional [csDMARDs] or targeted [tsDMARDs]) or biological (bDMARDs).

  Most of the clinical trials of newly developed agents, especially bDMARDs, have been in patients with longer-term disease, in whom other treatments have failed to control symptoms.

  However, in the light of research highlighting the extent of irreversible joint damage occurring in the early stages of rheumatoid arthritis, we have focused this overview on interventions in treatment-naïve patients and compared these with methotrexate or other csDMARDs (monotherapy or combinations).

  We evaluated evidence from RCTs and systematic reviews of RCTs.

- In people with rheumatoid arthritis of less than 2 years' duration who have not previously received any DMARD treatment:

  Adding other csDMARDs to methotrexate is unlikely to be beneficial compared with methotrexate monotherapy.

  We found no evidence from systematic reviews or RCTs meeting our inclusion criteria on which to judge the efficacy of bDMARDs as monotherapy compared with methotrexate or other csDMARDs in this population.

  Adding some bDMARDs to methotrexate is likely to have a beneficial effect on joint damage, clinical symptoms, and functional ability compared with methotrexate monotherapy, but this needs to be balanced against any increase in adverse effects. We found no evidence from systematic reviews or RCTs meeting our inclusion criteria on which to judge the efficacy of many other bDMARDs.

  Adding glucocorticoids (either as low dose or initially in high dose rapidly reducing to low dose) to methotrexate (or other csDMARDs or combination of csDMARDs, including methotrexate) has a beneficial effect on joint damage, clinical symptoms, and function.

Clinical context

GENERAL BACKGROUND

Rheumatoid arthritis is a chronic autoimmune disease, which most often presents as a symmetrical polyarthritis of the hands and feet. The symptoms of episodic joint pain and stiffness are exacerbated by rest and improved by movement. There is associated swelling and warmth of the affected joints due to inflammation of the synovium (synovitis). Treatments are classified as non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen), glucocorticoids (GCs, such as prednisolone or prednisone, which are biologically equivalent) and other disease-modifying anti-rheumatoid drugs, so called because they reduce the acute phase response and radiological joint damage (DMARDs, such as methotrexate and intramuscular gold). Recommendations regarding the treatment of newly diagnosed rheumatoid arthritis have changed frequently over the last 20 years; as new therapeutic agents have emerged, old ones have been re-evaluated and new evidence has accumulated. Methotrexate has become the most widely prescribed DMARD, and the UK National Institute for Health and Care Excellence (NICE) has recommended a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment. [1] In routine clinical practice, many patients are treated with many different individual and combination therapies. Biological DMARDs, developed over the last 15 years, are (generally) specially prepared antibodies derived from biological processes. This and other drug developments have resulted in a nomenclature system for these drugs [2] that has been used in this overview as follows: DMARDs are synthetic (that is, small chemical molecules; sDMARDs) or biological (usually modified antibodies; bDMARDs). Synthetic DMARDs are either conventional (that is, their precise mode of action is not known and they have been in use for many years; csDMARDs) or targeted (that is they were developed to target a specific cellular activity; tsDMARDs). Biological DMARDs are original (that is, developed specifically under particular conditions; boDMARDs) or 'biosimilar' (that is, developed to be similar to a boDMARD but not necessarily under the same conditions; bsDMARDs).

FOCUS OF THE REVIEW

The past two decades have shed light on the extent of irreversible joint damage occurring in the early stages of rheumatoid arthritis, [3] [4] but most of the clinical trials of newly developed agents, especially bDMARDs, have been in patients with longer-term disease in whom other treatments have failed to control symptoms. Therefore, this overview examines the evidence for the best first-line treatment for early rheumatoid arthritis. We focus on treatment-naïve patients to allow generalisability to the population of newly diagnosed patients.

COMMENTS ON EVIDENCE

All the trial data reported in this overview were gathered from participants who met (or are extremely likely to have met) the 1987 American Rheumatism Association (ARA; now the American College of Rheumatology [ACR]) criteria for rheumatoid arthritis, and all had current signs of active disease (defined in a variety of ways in different studies). The trial data were also taken from patients who had not been previously treated with csDMARDs (for >1 month) or bDMARDs. The overview results are, therefore, generalisable to the initiation of first-line treatment in people with newly diagnosed rheumatoid arthritis who fulfil the ARA 1987 criteria. Some studies excluded people who were thought to be at risk of certain adverse events or who had certain comorbidities, but many did not do so.

SEARCH AND APPRAISAL SUMMARY

The literature search for this overview was carried out from the start of each database searched up to December 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 2058 studies. Of the full articles evaluated, 10 systematic reviews, 22 RCTs, and one follow-up report were added at this update.

DEFINITION

Rheumatoid arthritis is a chronic autoimmune disorder. It is characterised by pain and swelling that primarily affects the peripheral joints and related peri-articular tissues. The hallmark presentation is as an insidious symmetrical polyarthritis of the hands and feet, often with non-specific symptoms such as malaise and fatigue. Conventionally, early rheumatoid arthritis is considered to be within the first 2 years of symptom onset. Blood tests show a raised acute phase response, and serum auto-antibodies are present in about 70% of patients: rheumatoid factors (RF) and anticitrullinated protein antibodies (ACPA). In most patients, progressive radiographic joint damage occurs, causing joint erosions, joint space narrowing, and subluxation. The inflammation and accumulating joint damage lead to progressive loss of function. The initial diagnosis of rheumatoid arthritis involves the amalgamation of clinical symptoms and signs, serology, inflammatory markers, and radiographic features while being mindful of seronegative rheumatoid arthritis, early disease prior to the onset of radiographic features, and atypical clinical presentations. The most widely used classification criteria for rheumatoid arthritis were initially proposed in 1987 by the American Rheumatism Association (ARA; now the American College of Rheumatology [ACR]), [5] and the majority of clinical trials include patients meeting the ARA 1987 criteria. Disease activity is commonly measured using the Disease Activity Score (DAS), [6] which is also used to monitor response to treatment and inform thresholds for treatment escalation. Response to treatment is also measured using the ACR50 (or ACR20 or ACR70) criteria, [7] in which there is a 50% (or 20% or 70%) improvement in a specified range of clinical assessments. In the UK (and many other countries), the diagnosis and treatment of rheumatoid arthritis is undertaken by specialist rheumatologists. **Pharmacological treatments** include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) and other disease-modifying anti-rheumatoid drugs (DMARDs), which may be synthetic (either conventional [csDMARDs] or targeted [tsDMARDs]) or biological (bDMARDs). For this overview, we have examined the relative efficacy of csDMARDs, GCs, and bDMARDs in: achieving disease control; preventing radiographic progression using the change in modified total Sharp Score (mTSS) [8] or its nearest equivalent; improving symptoms using the ACR50 or its nearest equivalent; and functional ability using the Health Assessment Questionnaire Disability Index (HAQ-DI). [9]

INCIDENCE/ PREVALENCE

The overall world prevalence of rheumatoid arthritis is 0.37% to 1.25%. Women have a higher prevalence of this disease than men (0.75% and 0.16%, respectively). [10] Overall European prevalence is 0.62%, while in the UK it is 0.81% (1.16% in women and 0.44% in men). [11] [12] A study from the US found that recent years have seen a 2.5% per year rise in the incidence of rheumatoid arthritis in women but not in men. [13] A British study found the overall incidence to be 40/100,000 (54/100,000 for women and 25/100,000 for men) using the 2010 ACR/EULAR criteria, compared to 32/100,000 (45/100,000 for women and 18/100,000 for men) using the 1987 ACR criteria. [14]

AETIOLOGY/ RISK FACTORS

The aetiology of rheumatoid arthritis has long been elusive. Female sex, family history, hormonal changes, infection, ethnicity, smoking, and rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA) positivity are established risk factors for developing the disease. Emerging evi-

dence highlights the interplay between genetic and epigenetic factors in the aetiology of rheumatoid arthritis. [15]

PROGNOSIS

Rheumatoid arthritis follows a remitting and relapsing course. Early age of disease onset, treatment delay beyond 3 to 6 months from symptom onset, large number of joints involved, extra-articular and systemic features, female sex, HLA DRB1 *04/04 genotype, the presence of RF and ACPA, chronic anaemia, high C1q levels, and early radiographic joint damage carry a poor prognosis. [3] [4] [16] [17] [18] Work disability in early rheumatoid arthritis is reported as 10% to 30%. [10] [19] The leading cause of increased mortality in rheumatoid arthritis is cardiovascular disease, followed by infection, respiratory disease, and malignancy. A longitudinal cohort study of 1010 patients in the UK demonstrated reduced life expectancy (standardised all-cause mortality among men: 1.45, 95% CI 1.22 to 1.71; standardised all-cause mortality among women: 1.84, 95% CI 1.64 to 2.05) and higher cardiovascular mortality (standardised cardiovascular mortality among men: 1.36, 95% CI 1.04 to 1.75; standardised cardiovascular mortality among women: 1.93, 95% CI 1.65 to 2.26) in people with the disease. [20] A study of patients with early rheumatoid arthritis from 1990 to 2011 found that mortality rates had not improved over the past 20 years. [21] Data from the German biologics register, however, demonstrated reduced risk of mortality with good disease control. [22]

AIMS OF INTERVENTION

Intervention aims to induce disease remission, and prevent joint damage and consequent disability, while minimising adverse effects and thus maintaining physical function and quality of life. Therefore, intervention in rheumatoid arthritis is multifactorial, including effective drug treatment, patient education, physiotherapy, occupational therapy, and psychological support.

OUTCOMES

Symptom severity (joint damage) radiological erosions (e.g., measured by modified total Sharp Score [mTSS] or Larsen score); ultrasound measurement of synovitis; **symptom severity (clinical symptoms)**, including as measured by validated scales, such as the American College of Rheumatology response criteria (e.g., ACR50), Disease Activity Score, European League Against Rheumatism response criteria; or, where these were not reported, pain scores; early morning stiffness; tender joint count, swollen joint count, or both as assessed by an appropriate articular index; **symptom severity (function)** overall function as measured by validated scales, such as the Health Assessment Questionnaire Disability Index (HAQ-DI); **adverse effects** (withdrawals due to adverse effects; total number of reported adverse effects).

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date December 2014. Databases used to identify studies for this systematic overview include: Medline (1965 to December 2014), Embase (1947 to December 2014), and The Cochrane Database of Systematic Reviews (1966 to December 2014). **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English and containing 20 or more individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. The agreed study population criteria for inclusion in this overview were adults over the age of 18 with early rheumatoid arthritis (i.e., who met the ARA 1987 criteria for rheumatoid arthritis and had disease duration <2 years) where at least 80% of patients in the study had not received DMARD treatment for more than 1 month before randomisation ('DMARD naïve'). For studies where less than 80% but not all patients in the study were DMARD naïve, authors and pharmaceutical companies holding the data were contacted to provide data on the DMARD-naïve population. **Evidence evaluation** The principal outcome measures extracted for time points at approximately 6, 12, and 24 months (if available) were: x-ray damage to joints shown by change in the modified total Sharp Score (mTSS) or its nearest equivalent or (for one study) change in an ultrasound assessment of joints; change in symptoms shown by the proportion of patients achieving ACR50 or its nearest equivalent; and functional ability shown by change in the HAQ-DI. Other outcomes directly relevant to these three categories were noted. X-ray damage to joints is of particular interest as it correlates with longer term disability, [23] [24] [25] and there may be irreversible joint damage in the early stages of disease. [3] [4] Each author independently reviewed the full list of titles and abstracts of the search and obtained a full text copy of the studies potentially relevant for this overview. The authors then agreed the list of studies included in this overview, including studies where less than 80% but not all patients in the study were DMARD naïve. Each author independently extracted data from the studies according to a predefined data extraction form created on a spread sheet. They then independently verified each other's data extraction. Disagreements were settled by discussion and examination of the relevant text to reach a consensus. All data relevant to this overview were extracted from the included studies into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section

may have been reported in the 'Further information on studies' or 'Comment' sections (see below). **Adverse effects** were recorded based on the proportion of withdrawals because of an adverse effect and the total number of reported adverse effects. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** To aid readability of the numerical data in our overviews, we have rounded many percentages to one decimal place. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). The expert contributors have on occasion calculated some figures from the charts and graphs provided in the publication. Where this has been done, this has been clearly indicated in the data tables. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 56). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of methotrexate in combination with other csDMARDs versus methotrexate monotherapy in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)?**

OPTION **METHOTREXATE PLUS OTHER CSDMARD THERAPY VERSUS METHOTREXATE MONOTHERAPY** New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- The addition of conventional synthetic disease-modifying anti-rheumatoid drugs (csDMARDs) to methotrexate may result in no additional benefit compared with methotrexate alone in terms of effect on severity of clinical symptoms, the progression of radiographically diagnosed joint damage, and deterioration in function (as measured by disability scores) in people with rheumatoid arthritis who have not previously received any DMARD treatment.
- Any marginal benefit for combination therapy would have to be set against the increased occurrence of adverse effects.

Benefits and harms

Methotrexate plus other csDMARD therapy versus methotrexate monotherapy:

We found six systematic reviews. [26] [27] [28] [29] [30] [31] The first review [26] evaluated the efficacy and toxicity of methotrexate monotherapy compared with methotrexate in combination with csDMARDs. The second review [27] presented a meta-analysis of the effects of csDMARDs, glucocorticoids, and biologically original DMARDS (boDMARDs) on radiographic joint destruction. The third review [28] assessed the efficacy on signs and symptoms, disability, and structure of all the then available DMARDs. The focus was on mono- and combination therapy but disregarded the addition of biological agents or glucocorticoids. The fourth review [29] is an update of the third review. It specifically examined methotrexate monotherapy versus its combination with other csDMARDs. The fifth review [30] examined effective strategies for the treatment of rheumatoid arthritis. Many such strategies had an early treatment period where methotrexate was compared with placebo or other csDMARD, but the overall study results related to the overall treatment strategy. A further update [29] examined csDMARDs, glucocorticoids, and tofacitinib. The last review [31] undertook a network meta-analysis of a variety of therapies, including combinations with methotrexate, and analysed their effect on joint destruction. The last complete search date from these reviews was January 2013. We identified eight RCTs that met the criteria for inclusion for this overview. [32] [33] [34] [35] [36] [37] [38] [39]

Symptom severity (joint damage)

Methotrexate plus other csDMARD therapy compared with methotrexate monotherapy Combination treatment with methotrexate plus another csDMARD may be no more effective than methotrexate alone at reducing the progression

of radiographically diagnosed joint damage in people with rheumatoid arthritis who have not previously received any DMARD treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (joint damage)					
[32] RCT **3-armed trial**	205 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean change in x-ray total damage score (modified Sharp score) , 1 year** 3.46 with methotrexate plus sulfasalazine 4.50 with methotrexate plus placebo 137 people allocated to either of these 2 arms Analysis in 98 people (only those with available x-rays) The remaining arm included people treated with sulfasalazine	Reported as not significant	⟷	Not significant
[33] RCT	61 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean change in x-ray damage score (modified Sharp score) , 1 year** 1.93 with methotrexate plus ciclosporin A 7.47 with methotrexate 58 people in this analysis	P = 0.018	○○○	methotrexate plus ciclosporin A
[34] RCT	160 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean yearly rate of progression in x-ray damage score (Larsen score) , 1 year** –0.2 with methotrexate plus ciclosporin +0.4 with methotrexate plus placebo 157 people in this analysis Patients also received intra-articular betamethasone (see Further information on studies)	Reported as not significant	⟷	Not significant

Symptom severity (clinical symptoms)

Methotrexate plus other csDMARD therapy compared with methotrexate monotherapy Combination treatment with methotrexate plus another csDMARD may be no more effective than methotrexate alone at reducing severity of clinical symptoms in people with rheumatoid arthritis who have not previously received any DMARD treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (clinical symptoms)					
[35] RCT **3-armed trial**	105 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR20 response) , 12 months** 78% with methotrexate plus sulfasalazine 71% with methotrexate plus placebo The remaining arm evaluated people treated with sulfasalazine only 71 people in this analysis	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[32] RCT **3-armed trial**	205 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR20 response) , 12 months** 65% with methotrexate plus sulfasalazine 59% with methotrexate plus placebo The remaining arm evaluated people treated with sulfasalazine 137 people in this analysis	Reported as not significant	⟷	Not significant
[33] RCT	61 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR50 response) , 12 months** 15/30 (50%) with methotrexate plus ciclosporin A 13/31 (42%) with methotrexate 61 people in this analysis	Reported as not significant	⟷	Not significant
[34] RCT	160 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR50 response) , 12 months** 63% with methotrexate plus ciclosporin 55% with methotrexate plus placebo Absolute results reported graphically 160 people in this analysis Participants also received intra-articular betamethasone (see Further information on studies)	Reported as not significant	⟷	Not significant
[36] RCT **3-armed trial**	66 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR50 response) , 24 months** 10/24 (42%) with methotrexate plus high-dose doxycycline 3/24 (13%) with methotrexate plus placebo Remaining arm evaluated methotrexate plus low-dose doxycycline Numbers completing the trial: 8/24 for methotrexate plus placebo; 12/24 for methotrexate plus high-dose doxycycline (see Further information on studies)	P = 0.02	○○○	methotrexate plus doxycycline (high dose)
[36] RCT **3-armed trial**	66 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR50 response) , 24 months** 17/42 (41%) with methotrexate plus doxycycline (combined high-dose and low-dose doxycycline plus methotrexate arms) 3/24 (13%) with methotrexate plus placebo High loss to follow-up (see Further information on studies)	P = 0.03	○○○	methotrexate plus doxycycline (low and high dose combined)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[37] RCT **3-armed trial**	281 people with 'high risk' of progressing to persistent arthritis who had not been treated with disease-modifying anti-rheumatic drugs Subgroup analysis	**Proportion showing improvement (ACR50 response) , 3 months** 85% with methotrexate plus sulfasalazine plus hydroxychloroquine 76% with methotrexate Both interventions above were also taking tapering doses of oral glucocorticoids (see Further information on studies) Remaining arm evaluated methotrexate plus sulfasalazine plus hydroxychloroquine plus intramuscular glucocorticoids 114 people in this analysis			
[38] RCT **4-armed trial**	755 people with early active rheumatoid arthritis almost all of whom had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR50 response) , 6 months** 55% with methotrexate plus sulfasalazine plus hydroxychloroquine 36% with methotrexate (2 arms combined) Absolute results reported graphically These percentages were calculated by the contributors of this overview from the graphical data The remaining arm evaluated immediate treatment with methotrexate plus etanercept 511 people in this analysis	P = 0.0022 This P value has been calculated by the expert contributors of this overview	○○○	methotrexate plus sulfasalazine plus plus hydroxychloroquine
[39] RCT **3-armed trial**	290 'high risk' people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (good EULAR response) , 4 months** 79.6% with methotrexate plus glucocorticoids 79.6% with methotrexate plus glucocorticoids plus sulfasalazine 76.6% with methotrexate plus glucocorticoids plus leflunomide 196 people in this analysis See Further information on studies	P = 0.84 Among-group analysis		

Symptom severity (function)

Methotrexate plus other csDMARD therapy compared with methotrexate monotherapy Combination treatment with methotrexate plus another csDMARD may be no more effective than methotrexate alone at reducing deterioration in function (as measured by disability scores) in people with rheumatoid arthritis who have not previously received any DMARD treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (function)					
[35] RCT	105 people with early active rheumatoid arthritis	**Mean reduction in disability score (HAQ) , 12 months**	Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	who had not been treated with disease-modifying anti-rheumatic drugs	0.51 with methotrexate plus sulfasalazine 0.46 with methotrexate plus placebo The remaining arm evaluated people treated with sulfasalazine only 71 people in this analysis			
[32] RCT **3-armed trial**	205 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean reduction in disability score (HAQ) , 12 months** 0.70 with methotrexate plus suphasalazine 0.73 with methotrexate plus placebo The remaining arm evaluated people treated with sulfasalazine 137 people in this analysis	Reported as not significant	⟷	Not significant
[34] RCT	160 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion with low disability score (HAQ equal to or <0.25) , 12 months** 47/80 (59%) with methotrexate plus ciclosporin 35/80 (44%) with methotrexate plus placebo Patients also received intra-articular betamethasone (see Further information on studies)	P = 0.08	⟷	Not significant
[36] RCT **3-armed trial**	66 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean reduction in disability score (HAQ) , 24 months** 0.47 with methotrexate plus doxycycline (combined high-dose and low-dose doxycycline plus methotrexate arms) 0.28 with methotrexate plus placebo Numbers completing the trial at 2 years: 8/24 for methotrexate plus placebo; 12/24 for methotrexate plus high-dose doxycycline; 7/18 for low-dose doxycycline plus methotrexate (see Further information on studies)	Reported as not significant	⟷	Not significant
[37] RCT **3-armed trial**	281 'high risk' patients with early active rheumatoid arthritis (according to the 1987 ACR criteria) who had not been treated with disease-modifying anti-rheumatic drugs Subgroup analysis	**Mean reduction in disability score (HAQ) , 3 months** 0.47 with methotrexate plus sulfasalazine plus hydroxychloroquine 0.42 with methotrexate Both interventions above were also taking tapering doses of oral glucocorticoids (see Further information on studies) The remaining arm evaluated methotrexate plus sulfasalazine plus hydroxychloroquine plus intramuscular glucocorticoids 99 people in this analysis	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[38] RCT **4-armed trial**	755 people with early active rheumatoid arthritis, almost all of whom had not been treated with disease-modifying anti-rheumatic drugs	**Mean reduction in disability score (MHAQ) , 6 months** with methotrexate plus sulfasalazine plus hydroxychloroquine with methotrexate (2 arms combined) The remaining arm evaluated immediate treatment with methotrexate plus etanercept 511 people in this analysis	Reported as "similar"		
[39] RCT **3-armed trial**	290 'high risk' patients with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion with a clinically meaningful HAQ response (as defined in the trial) , 4 months** 87% with methotrexate plus glucocorticoids (as reported in the narrative; differently reported in the table [76.5%]) 85% with methotrexate plus glucocorticoids plus sulfasalazine 77% with methotrexate plus glucocorticoids plus leflunomide 290 people in this analysis See Further information on studies.	P = 0.27 among groups		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawals due to adverse effects					
[35] RCT **3-armed trial**	105 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects** 5/36 (14%) with methotrexate plus sulfasalazine 2/35 (6%) with methotrexate plus placebo The remaining arm evaluated people treated with sulfasalazine only 71 people in this analysis	Reported as "not different"		
[32] RCT **3-armed trial**	205 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects** 9/68 (13%) with methotrexate plus sulfasalazine 7/69 (10%) with methotrexate plus placebo The remaining arm evaluated people treated with sulfasalazine 137 people in this analysis			
[33] RCT	61 people with early active rheumatoid arthritis who had not been treated with disease-	**Patients withdrawn due to adverse effects , 12 months** 7/30 (23%) with methotrexate plus ciclosporin A			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	modifying anti-rheumatic drugs	2/31 (6%) with methotrexate			
[34] RCT	160 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects , 12 months** 1/80 (1%) with methotrexate plus ciclosporin 3/80 (4%) with methotrexate Patients also received intra-articular betamethasone (see Further information on studies)			
[36] RCT **3-armed trial**	66 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects , 24 months** 4/24 (17%) with methotrexate plus high-dose doxycycline 2/24 (8%) with methotrexate plus placebo The remaining arm evaluated methotrexate plus low-dose doxycycline			
[36] RCT **3-armed trial**	65 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects , 24 months** 6/42 (14%) with methotrexate plus doxycycline (combined high-dose and low-dose doxycycline plus methotrexate arms) 2/24 (8%) with methotrexate plus placebo			
[37] RCT **3-armed trial**	281 people with 'high risk' of progressing to persistent arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects , 3 months** 0/93 (0%) with methotrexate plus sulfasalazine plus hydroxychloroquine 3/97 (3%) with methotrexate Participants in both interventions were also taking tapering doses of oral glucocorticoids (see Further information on studies) The remaining arm evaluated methotrexate plus sulfasalazine plus hydroxychloroquine plus intramuscular glucocorticoids			
[39] RCT **3-armed trial**	290 'high risk' people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects** 2/98 safety failures (2%) with methotrexate plus sulfasalazine plus glucocorticoids 1/98 (1%) with methotrexate plus glucocorticoids The remaining arm evaluated methotrexate plus glucocorticoids plus leflunomide			
[39] RCT **3-armed trial**	290 'high risk' people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Patients withdrawn due to adverse effects** 0/94 (0%) with methotrexate plus leflunomide plus glucocorticoids 1/98 (1%) with methotrexate plus glucocorticoids			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arm evaluated methotrexate plus sulfasalazine plus glucocorticoids			
Total reported adverse effects					
[35] RCT **3-armed trial**	105 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with 1 or more adverse effects** 32/36 (89%) with methotrexate plus sulfasalazine 27/35 (77%) with methotrexate plus placebo			
[32] RCT **3-armed trial**	205 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with 1 or more adverse effects** 91% with methotrexate plus sulfasalazine 75% with methotrexate plus placebo The remaining arm evaluated people treated with sulfasalazine	P = 0.013 P value calculated by the authors of this overview	○○○	methotrexate
[33] RCT	61 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with 1 or more adverse effects** 67% with methotrexate plus ciclosporin A 55% with methotrexate			
[34] RCT	160 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Total adverse effects/total number of patients for adverse effects occurring in >10% of either group** 1.11 with methotrexate plus ciclosporin 0.79 with methotrexate Calculated by the contributors of this overview Patients also received intra-articular betamethasone (see Further information on studies)	P <0.001 P value calculated by the authors of this overview	○○○	methotrexate
[37] RCT **3-armed trial**	281 people with 'high risk' of progressing to persistent arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with 1 or more adverse effect** 75% with methotrexate plus sulfasalazine plus hydroxychloroquine 56% with methotrexate Participants in both interventions above were also taking tapering doses of oral glucocorticoids (see Further information on studies) The remaining arm evaluated methotrexate plus sulfasalazine plus hydroxychloroquine plus intramuscular glucocorticoids	P = 0.006	○○○	methotrexate
[38] RCT **4-armed trial**	755 people with early active rheumatoid arthritis, almost all of whom had not been treated with disease-modifying	**Proportion of patients with 1 or more adverse effect** 77% with methotrexate plus sulfasalazine plus hydroxychloroquine 74% with methotrexate (2 arms combined)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	anti-rheumatic drugs	The remaining arm evaluated immediate treatment with methotrexate plus etanercept 511 people in this analysis			
[39] RCT **3-armed trial**	290 'high risk' people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Total adverse effects/total number of patients for adverse effects occurring in first 16 weeks** 1.63 with methotrexate plus sulfasalazine plus glucocorticoids 1.43 with methotrexate plus leflunomide plus glucocorticoids 0.73 with methotrexate plus glucocorticoids	P = 0.006	○○○	methotrexate

Further information on studies

[35] This study was of complex design and included three arms. In the second arm, methotrexate was given at a dose of 7.5 mg/week (together with placebo tablets), and increased to 15 mg/week after 16 weeks if symptoms were poorly controlled, and replaced after 24 weeks if symptoms remained uncontrolled. In the third arm, methotrexate was given at a dose of 7.5 mg/week, and in addition sulfasalazine 500 mg twice daily, increasing to 1000 mg twice daily in 10 days. The treatment was increased to methotrexate 15 mg/week and sulfasalazine 1500 mg twice daily after 16 weeks if symptoms were poorly controlled, and replaced after 24 weeks if symptoms remained uncontrolled. The trial also included a sulfasalazine-only arm (the first arm), not reported in this overview. Medication increases were 11 for the methotrexate arm and 7 for methotrexate plus sulfasalazine. This bias is against the overall finding, and so the result can be included in this overview. No damage scores were reported. ACR20 was the reported clinical outcome that most closely resembled ACR50.

[32] This multi-centre RCT included three arms. It is reported as double-blind; although, one review described the methods of randomisation and allocation concealment as unclear. [26] In the second arm, methotrexate was given at a dose of 7.5 mg/week (together with placebo tablets) and increased to 15 mg/week after 16 weeks if symptoms were poorly controlled. In the third arm, methotrexate was given at a dose of 7.5 mg/week and, in addition, sulfasalazine 500 mg twice daily, increasing to 1000 mg twice daily in 10 days. The treatment was increased to methotrexate 15 mg/week and sulfasalazine 1500 mg twice daily after 16 weeks if symptoms were poorly controlled. The trial also included a sulfasalazine-only arm (the first arm). Medication increases would provide a bias against showing a significant benefit for any treatment arm. The mean change in total damage score showed a non-significant benefit in favour of combination therapy at 1 year. ACR20 was the reported clinical outcome that most closely resembled ACR50. The primary outcome of this study was change in the DAS28, and this was significantly in favour of combination therapy.

[33] In this single-blind comparison (in which radiographic joint damage measured by blinded assessors was the primary outcome, and the clinical assessor was blind to treatment allocation), randomisation was by a sealed envelope procedure. An initial dose of intramuscular methotrexate 10–15 mg/week (depending on the patient's weight) could be adjusted up (to 20 mg/week) or down to take account of symptoms and adverse effects. In the other arm of the study, to the methotrexate (same dose arrangements) was added oral ciclosporin A at 3 mg/kg/day, which could be adjusted up (to 4 mg/kg/day) or down to take account of symptoms and adverse effects. The actual dose received of ciclosporin A was slightly less at the end of the trial than at the start, the dose of methotrexate was slightly less at the end of the trial than at the start in the combination therapy arm, and the dose of methotrexate was slightly higher at the end of the trial than at the start in the methotrexate-only arm. Therefore, there is a treatment bias against the result showing a benefit for the combination arm. Concurrent corticosteroid therapy up to a maximum set dose was permitted. No functional assessments were reported.

[34] In this complex double-blind study comparing methotrexate plus placebo to methotrexate plus ciclosporin, patients in both treatment arms received multiple intra-articular injections of betamethasone to up to 4 swollen joints at each review visit, at the discretion of the managing physician. Methotrexate was given at a dose of 7.5 mg/week, but from week 8 onwards, and then every 4 weeks if swollen joints were present, it was increased by 2.5 mg/week (up to a maximum of 20 mg/week). Ciclosporin was given at 2.5 mg/kg body weight/day. After week 28, and then every 4 weeks, if swollen joints were present, the ciclosporin was increased by 0.5 mg/kg (up to a maximum of 4 mg/kg). The ciclosporin dose could also be reduced if specified adverse reactions occurred. By the end of

the study, the dose of methotrexate was lower in the combination arm, and the ciclosporin dose was increased in only 10% of the combination-arm patients. The number of intra-articular injections was higher in the methotrexate arm. Therefore, there is a treatment bias against the result showing a benefit for the combination arm. The radiographic outcome used was the Larsen score.

[36] In this double-blind study, two doses of doxycycline were compared with placebo in patients who were all also treated with methotrexate, given at a dose of 7.5 mg/week, every 3 months. If the ACR50 criteria were not met, it was increased up to a maximum of 17.5 mg/week (it could also be reduced if the ACR50 criteria were met). The doxycycline dose was 100 mg twice daily or 20 mg twice daily. Allocation to the low-dose arm was stopped part-way through the study. The final dose of methotrexate was not different between the three treatment arms, suggesting that no bias was introduced. No damage scores were reported. The ACR50 response was reported only at 2 years, when it showed a benefit in favour of combination therapy at 2 years in both the comparisons included in this review, but the authors comment that the low response rate in the methotrexate-only arm was surprising. Change in HAQ score at 2 years showed a non-significant benefit in favour of combination therapy at 2 years in both the comparisons included in this review. The proportion who withdrew due to adverse effects showed a non-significant benefit against combination therapy. The overall incidence of adverse effects is not reported.

[37] This complex single-blind study was directed at patients with early signs of inflammatory arthritis, only some of whom met the standard criteria for the diagnosis of rheumatoid arthritis. However, the results for these patients were reported separately, and it is those results that are included in this overview. In the two arms of the study that contribute to the present overview (arms 2 and 3), all patients were treated with tapering oral glucocorticoids. The taper consisted of 15 mg/day (it is not clear from the report which oral medication was used) for 4 weeks, then 10 mg per day for 2 weeks, then 5 mg per day for 2 weeks, then 2.5 mg/day for 2 weeks. In addition, second-arm patients were treated with methotrexate 25 mg/week and third-arm patients were treated with methotrexate 25 mg/week, sulfasalazine 2 g/day, and hydroxychloroquine 400 mg/day. After 12 weeks, in patients who had shown an inadequate response etanercept (a boDMARD) was added. Therefore, the results from only the first 12 weeks contribute to this review. The frequency of treatment increases in each group is not reported, but the study design would bias against finding the reported differences between treatment arms. No damage scores were reported.

[38] This complex double-blind study appears to include 25% of patients who had already been taking csDMARDs. However, in correspondence the author has indicated that, for all these patients, treatment had lasted less than 4 weeks before starting the trial. We have, therefore, included the study in our overview. Arms 3 and 4 of the study included methotrexate alone for the first 24 weeks, and the results have been combined for this overview. The methotrexate dose (initial dose not given) was either escalated to 20 mg/week or the dosage was lowered if treatment resulted in no active tender/painful or swollen joints by week 12. Arm 2 of the study added sulfasalazine 500 mg twice daily (escalated [if tolerated] to 1000 mg twice daily at 6 weeks) plus hydroxychloroquine 200 mg daily to the same methotrexate regimen. No information is available on the number of patients increasing their methotrexate dose during the first 24 weeks of the study, but the study design would bias against the reported differences between treatment arms. No damage scores were reported at 24 weeks. The proportion who withdrew due to adverse effects is not reported.

[39] This un-blinded 16-week RCT compared the early clinical response to three complex treatment regimens, which all included methotrexate plus glucocorticoids. The methotrexate dose was the same in each arm: 15 mg/week, but could be increased to 20 mg/week at 8 weeks if there was inadequate clinical response. In arm 1, the following were also used: sulfasalazine 2 g/day plus prednisone at the following doses (mg/day) for 1 week each: 60, 40, 25, 20, 15, 10, 7.5, then continued with 7.5 mg/day. In arm 2, the following was also used: prednisone at the following doses (mg/day) for 1 week each: 30, 20, 12.5, 10, 7.5, and 5 then continued with 5 mg/day. In arm 3, the following was also used: leflunomide 10 mg/day plus prednisone at the following doses (mg/day) for 1 week each: 30, 20, 12.5, 10, 7.5, 5, then continued with 5 mg/day. In practice there was no significant difference in treatment adjustments in the three arms, so it is unlikely that any bias was introduced. Recognising that the glucocorticoid regimen differed between arms 1 and 2, the authors of this overview nevertheless felt that the comparison with combination therapy was admissible to this overview. Arms 3 and 2 compared methotrexate (plus glucocorticoids) to leflunomide (plus the same dose of glucocorticoids). It is possible that a large effect of glucocorticoids could have dominated the outcome measured and resulted in bias against finding differences between treatment arms. No damage scores were reported.

Comment: Many studies reported appropriate outcomes at other time points. Only a small number of the potential combinations of methotrexate plus csDMARDs have been compared with methotrexate monotherapy. Very few of these trials show an unequivocal benefit for combination therapy, and such benefits are inconsistent between studies. Almost all studies report a greater incidence of adverse effects with combination therapy, some of which are statistically significant.

Clinical guide
Any marginal benefit for combination therapy would have to be set against the occurrence of adverse effects.

QUESTION **What are the effects of bDMARDs as monotherapy versus methotrexate or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)?**

OPTION **ABATACEPT MONOTHERAPY** New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of abatacept monotherapy as first-line treatment in early rheumatoid arthritis.

Benefits and harms

Abatacept monotherapy:

We found no RCT within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in monotherapy as a first-line treatment for early rheumatoid arthritis.

Comment: The AVERT study consisted of 351 patients with "early rheumatoid arthritis" and compared abatacept plus methotrexate versus abatacept monotherapy versus methotrexate monotherapy. [40] The criteria for diagnosing rheumatoid arthritis are not clear. Therefore, this study may have included early forms of other types of inflammatory arthritis. While it is stated that patients were methotrexate-naïve or had received methotrexate (<10 mg/week) for less than 4 weeks, there is no indication of their exposure to other conventional synthetic DMARDs (csDMARDs) or of the proportion of patients who are treatment-naïve at the point of randomisation. For these reasons, the trial was not included in the present overview.

Clinical guide
At present, there is no RCT evidence regarding the use of abatacept monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION **ANAKINRA MONOTHERAPY** New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of anakinra monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Anakinra monotherapy:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in monotherapy as a first-line treatment for early rheumatoid arthritis.

Comment: Regarding our overall clinical question, four RCTs included a bDMARD monotherapy arm but data on treatment-naïve patients were not separately published.

Clinical guide
At present, there is no RCT evidence regarding the use of anakinra monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION CERTOLIZUMAB MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of certolizumab monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Certolizumab monotherapy:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in monotherapy as a first-line treatment for early rheumatoid arthritis.

Comment: Regarding our overall clinical question, four RCTs included a bDMARD monotherapy arm but data on treatment-naïve patients were not separately published.

Clinical guide
At present, there is no RCT evidence regarding the use of certolizumab monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION INFLIXIMAB MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of infliximab monotherapy as first-line treatment in early rheumatoid arthritis.

Benefits and harms

Infliximab monotherapy:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in monotherapy as a first-line treatment for early rheumatoid arthritis.

Comment: Regarding our overall clinical question, four RCTs included a bDMARD monotherapy arm but data on treatment-naïve patients were not separately published.

Clinical guide
At present, there is no RCT evidence regarding the use of infliximab monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION RITUXIMAB MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of rituximab monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Rituximab monotherapy:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in monotherapy as a first-line treatment for early rheumatoid arthritis.

Comment: Regarding our overall clinical question, four RCTs included a bDMARD monotherapy arm but data on treatment-naïve patients were not separately published.

Clinical guide
At present, there is no RCT evidence regarding the use of rituximab monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION TOFACITINIB MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of tofacitinib monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Tofacitinib monotherapy:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in monotherapy as a first-line treatment for early rheumatoid arthritis.

Comment: Regarding our overall clinical question, four RCTs included a bDMARD monotherapy arm but data on treatment-naïve patients were not separately published.

Clinical guide
At present, there is no RCT evidence regarding the use of tofacitinib monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION ADALIMUMAB MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found insufficient evidence from RCTs and systematic reviews of RCTs on the use of adalimumab monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Adalimumab monotherapy:

We found no RCTs that met our inclusion criteria, but we found one RCT that included treatment-naïve patients within each arm of the study (see Comment section). [41] The results on the treatment-naïve patients have not been published separately.

Comment: The PREMIER study [41] examined 699 of 799 (87%) patients with early rheumatoid arthritis (symptom duration 2 years or less). The three arms of the study were adalimumab plus methotrexate, adalimumab monotherapy, and methotrexate monotherapy. Adalimumab was used at a dose of 40 mg every other week. Methotrexate was started at 7.5 mg/week and, if active disease was noted, it was increased to 15 mg/week by week 4–8 and then 20 mg/week by week 9. One third of patients had had previous conventional synthetic disease-modifying anti-rheumatoid drugs

(csDMARDs), and, therefore, 540 of 799 (68%) patients were treatment-naïve. Slightly more than one third in each study arm were on concomitant glucocorticoids (GCs).

This RCT demonstrated that, at 1 and 2 years of treatment, adalimumab plus methotrexate was superior to adalimumab monotherapy and methotrexate monotherapy at achieving ACR 50/70/90 responses (P <0.001) and 28-joint Disease Activity Score (DAS28) remission (P <0.001). Importantly, there is a statistically significant difference showing that methotrexate monotherapy is superior to adalimumab monotherapy at achieving ACR20 at 1 year (63% *v* 54%; P = 0.043). While a similar trend is maintained at 2 years for ACR20 and for achieving ACR50, 70, and 90 at both time points, the difference on these occasions is not statistically significant.

There was significantly less radiographic progression, measured by mean change in modified total Sharp score (mTSS), at 6 months, 1 year, and 2 years in the combination therapy arm compared with either monotherapy arm. The P values were less than 0.001 in all cases except for combination therapy compared with adalimumab monotherapy at 1 year, where P = 0.002. Adalimumab monotherapy was superior to methotrexate monotherapy at each of these time points (P <0.001). Combination therapy was also superior to either monotherapy arm at maintaining no radiographic progression (i.e., change in mTSS 0.5 or less; P <0.01). Adalimumab monotherapy was superior to methotrexate monotherapy (P <0.01) for this outcome.

At 1 year, the improvement in functional wellbeing (i.e., change in Health Assessment Questionnaire disability index [HAQ-DI]) was greater in the combination therapy arm compared with adalimumab monotherapy (P = 0.002) and compared with methotrexate monotherapy (P <0.001). At 2 years, combination was significantly better than methotrexate monotherapy (P <0.05) but not adalimumab monotherapy (P = 0.058).

Withdrawals due to adverse events and the proportion of participants experiencing serious adverse events were not significantly different between the three groups. One patient in the combination therapy, four patients in the adalimumab monotherapy, and one patient in the methotrexate monotherapy arm died during the study. The standardised mortality ratio of this study was 0.463 (95% CI 0.17 to 1.01).

Clinical guide
There is insufficient evidence to support the use of adalimumab monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION ETANERCEPT MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found insufficient evidence from RCTs and systematic reviews of RCTs on the use of etanercept monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Etanercept monotherapy:

We found no RCTs that met our inclusion criteria, but we found one RCT that included treatment-naïve patients within each arm of the study (see Comment section). [42] The results on the treatment-naïve patients have not been published separately.

Comment:

The ERA study [42] included 632 patients with early rheumatoid arthritis with a mean disease duration of 1 year. The three arms of the study were etanercept 25 mg twice-weekly monotherapy, etanercept 10 mg twice-weekly monotherapy, and methotrexate 7.5 mg weekly monotherapy. Methotrexate was increased to 15 mg by week 4 and 20 mg by week 8. One quarter of patients were on concomitant glucocorticoids (GCs). One quarter of patients in the etanercept monotherapy arm and just over one quarter of patients in the methotrexate monotherapy arm had had previous conventional synthetic disease-modifying anti-rheumatoid drug (csDMARD). Therefore, 368/632 (58%) of patients in this study were treatment-naïve.

This RCT demonstrated superiority of etanercept 25 mg twice weekly over methotrexate maximum 20 mg weekly at achieving ACR20 and ACR50 during the first 4 months of treatment (P <0.05) and ACR70 during the first 6 months of treatment (21% *v* 14%, calculated by the authors of this overview from the graph included in the reported RCT; P <0.05). However, the response rates were similar at 12 months.

Radiographic progression measured by mean rise in modified total Sharp score (mTSS) was significantly lower in the etanercept 25-mg group compared with the methotrexate group at 6 months (0.57 *v* 1.06; P = 0.001) but not at 12 months (1.00 *v* 1.59; P = 0.11). Significantly more patients in the etanercept 25-mg group had no increase in the erosion score at 12 months compared with the methotrexate group (72% *v* 60%; P = 0.007).

Methotrexate monotherapy was superior to etanercept 10 mg twice weekly at achieving ACR response and reducing radiographic progression.

Significantly more patients receiving methotrexate monotherapy withdrew due to adverse events compared with the etanercept 25 mg group (11% *v* 5%; P = 0.04). Injection site reactions, nausea, rash, alopecia, and mouth ulcers were significantly more common in the methotrexate group (P <0.05). No deaths were noted during this study.

Clinical guide
There is insufficient evidence to support the use of etanercept monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION GOLIMUMAB MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found insufficient evidence from RCTs and systematic reviews of RCTs on the use of golimumab monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Golimumab monotherapy:

We found no RCTs that met our inclusion criteria, but we found one RCT that included treatment-naïve patients within each arm of the study (see Comment section). [43] The results on the treatment-naïve patients have not been published separately.

Comment:

The GO BEFORE study [43] compared golimumab 100 mg monotherapy (group 1) with methotrexate monotherapy (group 2), golimumab 50 mg plus methotrexate (group 3), and golimumab 100 mg plus methotrexate (group 4) in people with active rheumatoid arthritis. During result analysis, the final group consisted of groups 3 and 4 in combination. Methotrexate was started at 10 mg weekly and titrated up to 20 mg by week 8.

In total, 387/637 (61%) had a disease duration of 2 years or less. However, 55% of the study population had had previous disease-modifying anti-rheumatoid drugs (DMARDs). Therefore, 290/637 (46%) were treatment naïve. A total of 67% were on glucocorticoids (GCs) at baseline.

The primary end point was not met, showing no significant difference in ACR50 at 24 weeks between the golimumab combined group (group 3 and group 4) and methotrexate monotherapy group (38% *v* 29%; P = 0.053). A post-hoc modified ITT analysis, which excluded three untreated patients, showed a significant difference in ACR50 between these two groups (39% in combined group *v* 29% methotrexate group; P = 0.049).

This RCT demonstrated no significant difference between golimumab monotherapy and methotrexate monotherapy at achieving ACR 20/50/70, EULAR good response, DAS28 (CRP) remission, and improvement in HAQ-DI.

Overall, occurrences of serious adverse events were similarly low across the treatment groups, with the exception of a higher incidence of serious infections in the golimumab 100 mg plus methotrexate group.

Clinical guide
There is insufficient evidence to support the use of golimumab monotherapy as a first-line treatment in early rheumatoid arthritis.

OPTION TOCILIZUMAB MONOTHERAPY New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found insufficient evidence from RCTs and systematic reviews of RCTs on the use of tocilizumab monotherapy as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Tocilizumab monotherapy:

We found no RCTs meeting our inclusion criteria and within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in monotherapy as a first-line treatment for early rheumatoid arthritis. We found one published abstract (see Comment section). [44]

Comment:

One study [44] published an abstract with data on 1157 patients with early rheumatoid arthritis, comparing tocilizumab 8 mg monotherapy with tocilizumab 8 mg plus methotrexate or tocilizumab 4 mg plus methotrexate or methotrexate monotherapy. All patients had a disease duration of 2 years or less. All patients were methotrexate naïve, but the number of patients who were treatment naïve is not stated.

At both 24 and 52 weeks, tocilizumab 8 mg plus methotrexate was significantly superior to methotrexate monotherapy at achieving DAS28-ESR remission (45% *v* 15% at 24 weeks and 49% *v* 20% at 52 weeks; P <0.0001). Tocilizumab 8 mg monotherapy was also superior to methotrexate monotherapy for this outcome (39% *v* 15%; p<0.0001 at 24 weeks and 39% *v* 20% at 52 weeks; P <0.0001 after hierarchical chain was broken).

A greater proportion of patients on tocilizumab 8 mg plus methotrexate achieved DAS28-ESR remission compared to tocilizumab 8 mg monotherapy (45% *v* 39% at 24 weeks and 49% *v* 39% at 52 weeks).

At week 52, tocilizumab 8 mg plus methotrexate was significantly better than methotrexate monotherapy at achieving ACR20/50/70 (P <0.05), reducing radiographic progression (mean mTSS at 52 weeks; P <0.05), and improving function (mean HAQ-DI at 52 weeks; P <0.05). Tocilizumab 8 mg monotherapy was numerically superior to methotrexate monotherapy but not statistically significant.

The frequency of adverse events was similar across treatment groups. The author of this RCT has advised the authors of this overview that the full publication of this RCT is pending.

Clinical guide
There is insufficient evidence to support the use of tocilizumab monotherapy as a first-line treatment in early rheumatoid arthritis.

QUESTION What are the effects of bDMARDs in combination with methotrexate versus methotrexate monotherapy or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)?

OPTION ABATACEPT PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .

- We found no direct evidence from RCTs regarding the role of abatacept in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Abatacept plus methotrexate:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in combination with methotrexate as a first-line treatment for early rheumatoid arthritis.

Comment:

The AVERT study included 351 patients with "early rheumatoid arthritis" and compared abatacept plus methotrexate versus abatacept monotherapy versus methotrexate monotherapy. [40] The criteria for diagnosing rheumatoid arthritis are not clear. Therefore, this study may have included early forms of other types of inflammatory arthritis. While it is stated that patients were methotrexate-naïve or had received methotrexate (<10 mg/week) for less than 4 weeks, there is no indication of their exposure to other conventional synthetic DMARDs (csDMARDs) or of the proportion of patients who are treatment-naïve at the point of randomisation. For these reasons, the trial was not included in the present overview.

Clinical guide

At present there is no RCT evidence to make any recommendation regarding the use of abatacept in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

OPTION ANAKINRA PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of anakinra in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Anakinra plus methotrexate:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in combination with methotrexate as a first-line treatment for early rheumatoid arthritis.

Comment:

Clinical guide

At present there is no RCT evidence regarding the use of anakinra in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

OPTION CERTOLIZUMAB PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of certolizumab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Certolizumab plus methotrexate:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in combination with methotrexate as a first-line treatment for early rheumatoid arthritis.

Comment: **Clinical guide**
At present there is no RCT evidence regarding the use of certolizumab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

OPTION TOFACITINIB PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found no direct evidence from RCTs regarding the role of tofacitinib in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Tofacitinib plus methotrexate:

We found no RCTs within our search dates that investigated the use of this biological disease-modifying anti-rheumatoid drug (bDMARD) in combination with methotrexate as a first-line treatment for early rheumatoid arthritis.

Comment: **Clinical guide**
At present there is no RCT evidence regarding the use of tofacitinib in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

OPTION ADALIMUMAB PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- Adalimumab in combination with methotrexate seems to have a substantial effect on disease activity and improving function in the first 6 months of treatment, and on reducing the rate of joint damage in the first 6 to 12 months, compared with methotrexate monotherapy.
- The benefit of adalimumab use needs to be balanced against the potential occurrence of serious adverse effects, particularly in older adults and those with comorbidities.

Benefits and harms

Adalimumab plus methotrexate versus methotrexate monotherapy:

We found three RCTs that met our criteria for inclusion. [45] [46] [47]

Symptom severity (joint damage)

Adalimumab plus methotrexate compared with methotrexate monotherapy Adalimumab plus methotrexate seems to be more effective than methotrexate monotherapy at reducing the proportion of people with radiographic progression of disease at 6 months to 48 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (joint damage)					
[45] RCT	1032 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <1 year (mean 4.25 months), 90%	**No radiographic progression (modified total Sharp score [mTSS]) , 6 months** 87% with adalimumab plus methotrexate 72% with placebo plus methotrexate	P <0.001	○○○	adalimumab plus methotrexate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	naïve to conventional synthetic disease-modifying anti-rheumatoid drugs (csDMARDs) and 100% naïve to biological DMARDs (bDMARDs) See Further information on studies	Absolute results reported graphically 1022 people in this analysis (n = 508 with adalimumab plus methotrexate; n = 514 with placebo plus methotrexate)			
[46] RCT	172 adults with rheumatoid arthritis (ARA 1987 criteria) with active disease, 100% csDMARD and bDMARD naïve	**No radiographic progression (mTSS) , week 48** 65% with adalimumab plus methotrexate 38% with placebo plus methotrexate Absolute numbers not reported The authors of this overview have calculated these percentages from the published cumulative probability chart Complete radiographic data available for 51 (59%) with adalimumab plus methotrexate; 47 (55%) with placebo plus methotrexate	P = 0.003	○○○	adalimumab plus methotrexate

Symptom severity (clinical symptoms)

Adalimumab plus methotrexate compared with methotrexate monotherapy Adalimumab plus methotrexate may be more effective than methotrexate monotherapy at reducing severity of clinical symptoms (ACR50 or DAS28 <2.6) at 6 months. The combination may also be effective at 1 year if used regularly rather than as an induction regimen (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (clinical symptoms)					
[45] RCT	1032 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <1 year (mean 4.25 months), 90% csDMARD naïve and 100% bDMARD naïve	**Proportion achieving ACR50 (using modified Total Sharp Score [mTSS]) , 6 months** 52% with adalimumab plus methotrexate 34% with placebo plus methotrexate Absolute results reported graphically 1032 people in this analysis (n = 515 with adalimumab plus methotrexate; n = 517 with placebo plus methotrexate)	P <0.001	○○○	adalimumab plus methotrexate
[46] RCT	172 adults with rheumatoid arthritis (ARA 1987 criteria) with active disease (mean baseline DAS28 [ESR] was 6.2), disease duration <1 year (mean 1.7 months), 100% csDMARD and bDMARD naïve	**Proportion achieving ACR50 , week 24** 64% with adalimumab plus methotrexate 49% with placebo plus methotrexate 155 people in this analysis	Difference (adjusted for status at baseline): –15.1 95% CI –29.3 to –0.3 P = 0.049	○○○	adalimumab plus methotrexate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[46] RCT	172 adults with rheumatoid arthritis (ARA 1987 criteria) with active disease (mean baseline DAS28 [ESR] was 6.2), disease duration <1 year (mean 1.7 months), 100% csDMARD and bDMARD naïve	**Proportion achieving ACR50 , week 48** 53% with adalimumab plus methotrexate 51% with placebo plus methotrexate 133 people in this analysis After 24 weeks, adalimumab and placebo injections were discontinued and methotrexate was continued in each arm (see Further information on studies)	Difference (adjusted for status at baseline): –1.2 95% CI –16.0 to +13.6 P = 0.88	⟷	Not significant
[47] RCT	180 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <6 months (mean 3 months), 100% csDMARD and bDMARD naïve	**Proportion achieving DAS28 <2.6 (remission) , 6 months** 62% with adalimumab plus methotrexate 46% with placebo plus methotrexate The authors of this overview have calculate the above percentages from the published bar chart (see Further information on studies)	P >0.05	⟷	Not significant
[47] RCT	180 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <6 months (mean 3 months), 100% csDMARD and bDMARD naïve	**Proportion achieving DAS28 <2.6 (remission) , 1 year** 74% with adalimumab plus methotrexate 49% with placebo plus methotrexate 161 people in this analysis (n = 81 with adalimumab plus methotrexate; n = 80 with placebo plus methotrexate); see Further information on studies	P = 0.0008	○○○	adalimumab plus methotrexate
[47] RCT	180 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <6 months (mean 3 months), 100% csDMARD and bDMARD naïve	**Proportion achieving ACR50 , 1 year** 80% with adalimumab plus methotrexate 63% with placebo plus methotrexate 161 people in this analysis (n = 81 with adalimumab plus methotrexate; n = 80 with placebo plus methotrexate); see Further information on studies	P = 0.02	○○○	adalimumab plus methotrexate

Symptom severity (function)

Adalimumab plus methotrexate compared with methotrexate monotherapy Adalimumab plus methotrexate may be more effective than methotrexate monotherapy at reducing decline in function (measured by HAQ-DI scores) at 6 months. The combination may also be effective at 1 year if used regularly rather than as an induction regimen (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (function)					
[45] RCT	1032 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease	**Proportion achieving normal function (i.e., HAQ-DI <0.5) , 6 months** 40% with adalimumab plus methotrexate	P <0.001	○○○	adalimumab plus methotrexate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	duration <1 year (mean 4.25 months), 90% csDMARD naïve and 100% bDMARD naïve	28% with placebo plus methotrexate Absolute results reported graphically 1032 people in this analysis (n = 515 with adalimumab plus methotrexate; n = 517 with placebo plus methotrexate)			
[46] RCT	172 adults with rheumatoid arthritis (ARA 1987 criteria) with active disease (mean baseline DAS28 [ESR] was 6.2), disease duration <1 year (mean 1.7 months), 100% csDMARD and bDMARD naïve	**Mean HAQ-DI , week 24** 0.49 with adalimumab plus methotrexate 0.72 with placebo plus methotrexate 155 people in this analysis	Difference (adjusted for status at baseline): 0.26 95% CI 0.10 to 0.42 P = 0.0014	○○○	adalimumab plus methotrexate
[46] RCT	172 adults with rheumatoid arthritis (ARA 1987 criteria) with active disease (mean baseline DAS28 [ESR] was 6.2), disease duration <1 year (mean 1.7 months), 100% csDMARD and bDMARD naïve	**Mean HAQ-DI , week 48** 0.61 with adalimumab plus methotrexate 0.66 with placebo plus methotrexate 133 people in this analysis After 24 weeks, adalimumab and placebo injections were discontinued and methotrexate was continued in each arm (see Further information on studies)	Difference = +0.082 95% CI –0.11 to +0.27 P = 0.4	⟷	Not significant
[47] RCT	180 adults with RA (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <6 months (mean 3 months), 100% csDMARD and bDMARD naïve	**Median change in HAQ-DI , 1 year** –0.88 with adalimumab plus methotrexate –0.63 with placebo plus methotrexate 161 people in this analysis (n = 81 with adalimumab plus methotrexate; n = 80 with placebo plus methotrexate); see Further information on studies	P = 0.012	○○○	adalimumab plus methotrexate

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawals due to adverse effects					
[45] RCT	1032 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <1 year (mean 4.25 months), 90% csDMARD naïve and 100% bDMARD naïve	**Proportion of patients withdrawn due to adverse effects** 21/515 (4%) with adalimumab plus methotrexate 16/517 (3%) with placebo plus methotrexate	P = 0.38 P value has been calculated by the authors of this overview	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[46] RCT	172 adults with rheumatoid arthritis (ARA 1987 criteria) with active disease (mean baseline DAS28 [ESR] was 6.2), disease duration <1 year (mean 1.7 months), 100% csDMARD and bDMARD naïve	**Proportion of patients withdrawn due to adverse effects , week 48** 4/87 (5%) with adalimumab plus methotrexate 7/85 (8%) with placebo plus methotrexate After 24 weeks, adalimumab and placebo injections were discontinued and methotrexate was continued in each arm (see Further information on studies)	P = 0.33 P value has been calculated by the authors of this overview	⟷	Not significant
[47] RCT	180 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <6 months (mean 3 months), 100% csDMARD and bDMARD naïve	**Proportion of patients withdrawn due to adverse effects , 12 months** 2/89 (2%) with adalimumab plus methotrexate 1/91 (1%) with placebo plus methotrexate See Further information on studies	P = 0.56 P value has been calculated by the authors of this overview	⟷	Not significant
Total reported adverse effects					
[45] RCT	1032 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <1 year (mean 4.25 months), 90% csDMARD naïve and 100% bDMARD naïve	**Proportion of patients with any adverse effect** 379/515 (74%) with adalimumab plus methotrexate 368/517 (71%) with placebo plus methotrexate	Reported as "similar between groups" P = 0.39 P value has been calculated by the authors of this overview	⟷	Not significant
[45] RCT	1032 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <1 year (mean 4.25 months), 90% csDMARD naïve and 100% bDMARD naïve	**Proportion of patients with serious adverse effect** 37/515 (7%) with adalimumab plus methotrexate 32/517 (6%) with placebo plus methotrexate 7 deaths were reported: 6 with adalimumab plus methotrexate, 1 with placebo plus methotrexate (see Further information on studies)	Reported as "similar between groups"		
[46] RCT	172 adults with rheumatoid arthritis (ARA 1987 criteria) with active disease (mean baseline DAS28 [ESR] was 6.2), disease duration <1 year (mean 1.7 months), 100% csDMARD and bDMARD naïve	**Proportion of patients with serious adverse effects** 12/87 (14%) with adalimumab plus methotrexate 22/85 (20%) with placebo plus methotrexate After 24 weeks, adalimumab and placebo injections were discontinued and methotrexate was continued in each arm (see Further information on studies)	P = 0.31 P value has been calculated by the authors of this overview	⟷	Not significant
[47] RCT	180 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 (CRP) >3.2 and disease duration <6 months	**Proportion of patients with serious adverse effects , 12 months** 14/89 (16%) with adalimumab plus methotrexate			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(mean 3 months), 100% csDMARD and bDMARD naïve	10/91 (11%) with placebo plus methotrexate See Further information on studies			

Further information on studies

[45] The OPTIMA trial compared adalimumab 40 mg every other week plus methotrexate with placebo plus methotrexate. In both groups methotrexate was titrated up to 20 mg/week by week 8. Concomitant systemic glucocorticoid use was comparable between the two groups (41% adalimumab *v* 46% placebo; no glucocorticoids 4 weeks prior to baseline). The primary end point was achievement of low disease activity (i.e., DAS28 <3.2) and no radiographic progression at week 78. ACR50 and HAQ-DI were measured as secondary end points. Patients were re-randomised after 26 weeks. Therefore, we have only included the 26-week (6 months) data in the present overview. The proportion of withdrawals due to adverse events and the proportion experiencing serious adverse events were similar between the two groups. Importantly, more deaths were observed in the adalimumab plus methotrexate group. The majority of these patients were of advanced age and had comorbidities.

[46] The HIT HARD study aimed to investigate whether induction therapy with adalimumab within the 'window of opportunity' in the rheumatoid arthritis disease process leads to long-lasting effects even when adalimumab is withdrawn. Participants had active disease (mean baseline DAS28 [ESR] was 6.2) and disease duration less than 1 year (mean 1.7 months). Fully 100% were csDMARD and bDMARD naïve. The RCT compared adalimumab 40 mg every other week plus methotrexate with placebo plus methotrexate. Patients in both groups received methotrexate 15 mg/week. At the end of 24 weeks of treatment, adalimumab and placebo injections were discontinued and all patients continued on methotrexate monotherapy. A stable dose of 10 mg or less prednisolone or equivalent was permitted, but there is no mention of the comparability between the two groups for this. The primary end point was DAS28 at week 48. While ACR50 and HAQ-DI were significantly better in the adalimumab group at the end of combination therapy (i.e., at week 24), this was not sustained following adalimumab withdrawal (i.e., at week 48). Interestingly, a higher proportion of patients in the methotrexate monotherapy group withdrew due to adverse effects. The same was found for the proportion experiencing overall serious adverse events (12/87 [14%] with adalimumab plus methotrexate *v* 22/85 [26%] with placebo plus methotrexate). No deaths were observed during the trial.

[47] The OPERA study compared adalimumab 40 mg every other week plus methotrexate with placebo plus methotrexate in people with early rheumatoid arthritis. Methotrexate was started at 7.5 mg/week and increased to 15 mg/week after 1 month and then to 20 mg/week by 2 months. The lead author of this RCT has confirmed that any swollen joints (up to 4 per visit) were injected with 0.5–2 mL of triamcinolone hexacetonide 20 mg/mL. No glucocorticoids (GCs) were used 4 weeks prior to baseline, but concomitant intra-articular GC use was permitted. The cumulative glucocorticoid dose and number of joints injected did not differ between the two arms of the study. The primary end point was low disease activity (DAS28 <3.2) at 12 months. DAS28-CRP remission, ACR50 at 1 year, and HAQ-DI were measured as secondary end points. Radiographic progression was not reported as part of this publication. While the proportions of withdrawals due to adverse events were similar between the two groups, a higher proportion in the adalimumab group experienced overall serious adverse events. No deaths were observed during the study.

Comment: For information on the PREMIER study, [41] please see the Comment section in the Adalimumab monotherapy option, p 17 .

The Yorkshire Early Arthritis Register Consortium RCT [48] consisted of 148 patients with early rheumatoid arthritis. It is unclear what proportion of patients were DMARD naïve. The study compared adalimumab 40 mg every other week plus methotrexate with placebo plus methotrexate. Methotrexate was started at 7.5 mg and increased to 25 mg by week 12 in the presence of residual synovitis. Prednisolone 10 mg or less/day was maintained. ACR50 and HAQ-DI were measured as secondary end points. The authors did not report on radiographic progression in this publication. A greater percentage of patients receiving adalimumab plus methotrexate achieved ACR50 compared with placebo plus methotrexate at 56 weeks (56% *v* 45%; P = 0.189), but this was not significant. Adalimumab plus methotrexate produced a significantly better improvement in HAQ-DI at 56 weeks compared with placebo plus methotrexate (–0.7 *v* –0.4; P = 0.005). The rate of withdrawals due to adverse events was lower in the adalimumab plus methotrexate group compared to the

methotrexate monotherapy group (8% *v* 11%). Serious adverse events were similar between the two groups.

The HOPEFUL 1 study [49] consisted of 334 patients with early rheumatoid arthritis and compared adalimumab 40 mg every other week plus methotrexate with placebo plus methotrexate. Methotrexate was initiated at 6 mg/week, and increased to 8 mg/week if there was a lack of more than 20% improvement in clinical synovitis by week 8. A total of 43% in the adalimumab plus methotrexate arm and 53% in the methotrexate monotherapy arm had had previous DMARDs. Therefore, 97/171 (57%) in the adalimumab group and 76/162 (47%) in the methotrexate monotherapy group would have fulfilled the inclusion criteria for this overview. The primary end point was inhibition of radiographic progression. ACR50 and HAQ-DI at 26 weeks were measured as secondary end points. Adalimumab plus methotrexate was superior to methotrexate monotherapy at inhibiting radiographic progression (62% *v* 35%; P = 0.001), achieving ACR50 (64% *v* 39%; P <0.001), and achieving normal functional status (60% *v* 37%; P <0.001). There were no significant differences between the rates of adverse events or withdrawals due to adverse events between the groups. One death was observed in the methotrexate monotherapy group.

Clinical guide

All three included studies found benefit in using adalimumab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis. The benefit of adalimumab use needs to be balanced against the potential occurrence of serious adverse effects, particularly in older adults and those with comorbidities.

OPTION ETANERCEPT PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- Etanercept in combination with methotrexate may reduce the rate of joint damage and disease activity and improve function in the first 6 to 12 months of treatment compared with methotrexate monotherapy.
- However, we only found one RCT that met the inclusion criteria of this overview.

Benefits and harms

Etanercept plus methotrexate versus methotrexate monotherapy:

We found one RCT [50] that met our inclusion criteria for inclusion. The lead author and the company holding the information have provided their data on the treatment-naïve patients included in the study. While radiographic progression, ACR50, and HAQ-DI were measured at 1 year, the latter two outcomes were also measured at 6 months.

Symptom severity (joint damage)

Etanercept plus methotrexate compared with methotrexate monotherapy Etanercept plus methotrexate may be more effective than methotrexate monotherapy at reducing mean change in joint damage (radiological) at 1 year (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (joint damage)					
[50] RCT	542 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 3.2 or greater, disease duration <2 years (mean 9 months), 79% naïve to conventional synthetic disease-modifying anti-rheumatoid drugs (csDMARDs), 100% naïve to biological DMARDs (bDMARDs) Subgroup analysis DMARD-naïve patients	**Mean change in modified Total Sharp Score (mTSS) , 1 year** 0.332 with etanercept plus methotrexate 2.541 with placebo plus methotrexate These data for csDMARD- and bDMARD-naïve patients were provided by the authors of this RCT	Difference = –2.209 95% CI –3.355 to –1.062 P = 0.0002	◌◌◌	etanercept plus methotrexate

Symptom severity (clinical symptoms)

Etanercept plus methotrexate compared with methotrexate monotherapy Etanercept plus methotrexate may be more effective than methotrexate monotherapy at reducing severity of clinical symptoms (ACR50) at 6 to 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (clinical symptoms)					
[50] RCT	542 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 3.2 or greater, disease duration <2 years (mean 9 months), 79% csDMARD naïve, 100% bDMARD naïve Subgroup analysis DMARD-naïve patients	**Proportion achieving ACR50 , 6 months** 68% with etanercept plus methotrexate 44% with placebo plus methotrexate These data for csDMARD- and bDMARD-naïve patients were provided by the authors of this RCT	Difference = 23.6% 95% CI 14.0 to 33.2% P <0.0001	○○○	etanercept plus methotrexate
[50] RCT	542 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 3.2 or greater, disease duration <2 years (mean 9 months), 79% csDMARD naïve, 100% bDMARD naïve Subgroup analysis DMARD-naïve patients	**Proportion achieving ACR50 , 1 year** 73% with etanercept plus methotrexate 50% with placebo plus methotrexate These data for csDMARD- and bDMARD-naïve patients were provided by the authors of this RCT	Difference = 22.8% 95% CI 13.3 to 32.2% P <0.0001	○○○	etancercept plus methotrexate

Symptom severity (function)

Etanercept plus methotrexate compared with methotrexate monotherapy Etanercept plus methotrexate may be more effective than methotrexate monotherapy at reducing decline in function (measured by HAQ-DI scores) at 6 to 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (function)					
[50] RCT	542 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 3.2 or greater, disease duration <2 years (mean 9 months), 79% csDMARD naïve, 100% bDMARD naïve Subgroup analysis DMARD-naïve patients	**Mean change in HAQ-DI , 6 months** 0.92 with etanercept plus methotrexate 0.68 with placebo plus methotrexate These data for csDMARD- and bDMARD-naïve patients were provided by the authors of this RCT	Difference = 0.239 95% CI 0.120 to 0.358 P <0.0001	○○○	etanercept plus methotrexate
[50] RCT	542 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 3.2 or greater, disease duration <2 years (mean 9 months),	**Mean change in HAQ-DI , 1 year** 1.004 with etanercept plus methotrexate 0.733 with placebo plus methotrexate	Difference = 0.271 95% CI 0.145 to 0.397 P <0.001	○○○	etanercept plus methotrexate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	79% csDMARD naïve, 100% bDMARD naïve Subgroup analysis DMARD-naïve patients	These data for csDMARD- and bDMARD-naïve patients were provided by the authors of this RCT			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawals due to adverse effects					
[50] RCT	542 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 3.2 or greater, disease duration <2 years (mean 9 months), 79% csDMARD naïve, 100% bDMARD naïve	**Proportion of patients withdrawn due to adverse effects , 1 year** 28/274 (10%) with etanercept plus methotrexate 34/268 (13%) with placebo plus methotrexate 1 death, but group remained blinded at time of publication	P = 0.36 P value has been calculated by the authors of this overview	⟷	Not significant
Total reported adverse effects					
[50] RCT	542 adults with rheumatoid arthritis (ARA 1987 criteria) with DAS28 3.2 or greater, disease duration <2 years (mean 9 months), 79% csDMARD naïve, 100% bDMARD naïve; no GC 4 weeks prior to baseline	**Proportion of patients suffering serious adverse effects , 1 year** 33/274 (12%) with etanercept plus methotrexate 34/268 (13%) with placebo plus methotrexate	P = 0.179 P value has been calculated by the authors of this overview	⟷	Not significant

Further information on studies

[50] This publication reports results from the first year of the COMET study. The RCT compared etanercept 50 mg weekly plus methotrexate with placebo plus methotrexate in early rheumatoid arthritis (disease duration <2 years). The criteria used to diagnose rheumatoid arthritis are not stated; however, the authors have confirmed that they were the ARA 1987 criteria. A total of 18% of the etanercept plus methotrexate group and 24% of the methotrexate monotherapy group had had previous DMARDs. Therefore, 226/274 (82%) of the etanercept plus methotrexate group and 203/268 (75%) of the methotrexate monotherapy group would have fulfilled the inclusion criteria for this overview. The lead author and the company holding the data on these patients has provided us with the radiographic, symptom, and functional ability data. In all patients, methotrexate was started at 7.5 mg weekly and titrated up to 20 mg in the presence of active disease. Treatment was continued for 52 weeks, but the study continued for 2 years. Participants had no GC 4 weeks prior to baseline. Concomitant systemic GC use (10 mg/day or less prednisolone or equivalent) at a stable dose was permitted during the first 24 weeks and titrated down thereafter. There is no comment on the comparability between the GC use in the two arms. The co-primary endpoints were; achievement of DAS28 remission and change in modified total Sharp score (mTSS) at 52 weeks. There was significantly less radiographic progression, greater proportion achieving ACR50, and greater improvement in HAQ-DI in the etanercept plus methotrexate group compared to the methotrexate monotherapy group. Data supplied by the authors for changes in Total Sharp Score at 52 weeks were: etanercept plus methotrexate 0.332; methotrexate monotherapy 2.541; P = 0.0002. Data supplied by the authors for the proportion of patients with ACR50 response were: etanercept plus methotrexate 67.8% and 72.5% at 24 weeks

and 52 weeks; methotrexate monotherapy 44.2% and 49.7% at 24 weeks and 52 weeks (P <0.001 at both time points). Data supplied by the authors for the HAQ scores at baseline, 24 weeks, and 52 weeks were: etanercept plus methotrexate 1.70, 0.73, and 0.64; methotrexate monotherapy 1.64, 0.94, and 0.89 (P <0.001 for 24 and 52 weeks). The proportions of withdrawals due to adverse events and of overall serious adverse events were similar between the two groups. This was also the case for the proportion experiencing any adverse event (90% etanercept plus methotrexate *v* 92% methotrexate monotherapy). One death was observed, but the group with this patient remained blinded at publication.

Comment: The EMPIRE trial [51] studied the use of etanercept in combination with methotrexate in patients to induce remission in early arthritis. While all the included patients were treatment naïve, their diagnosis was of inflammatory arthritis rather than early rheumatoid arthritis; therefore, this trial would have contained patients who did not have rheumatoid arthritis. For this reason, the trial was not included in the present overview.

Clinical guide
Previously unpublished data from the included RCT shows benefit in using etanercept in combination with methotrexate as first-line treatment in early rheumatoid arthritis, with no evidence of increased risk of adverse effects compared with methotrexate monotherapy.

OPTION GOLIMUMAB PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found insufficient direct evidence from RCTs to support the use of golimumab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Golimumab plus methotrexate:

We found no RCTs that met our inclusion criteria, but we found one RCT that included treatment-naïve patients within each arm of the study (see Comment section). The results on the treatment-naïve patients have not been published separately.

Comment: For information on the RCT found, [43] please see the Comment section for Golimumab monotherapy, p 19 .

Clinical guide
There is insufficient evidence to support the use of golimumab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

OPTION INFLIXIMAB PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We only found one RCT
- Infliximab in combination with methotrexate may have a beneficial effect on reducing the rate of joint damage and disease activity and improving function in the first 6 to 12 months of treatment compared with methotrexate plus methylprednisolone.
- Any benefits must be weighed against the increased risk of adverse events occurring with infliximab.

Benefits and harms

Infliximab plus methotrexate versus methotrexate monotherapy:

The comparisons for this option of infliximab plus methotrexate included: methotrexate alone; other conventional disease-modifying anti-rheumatoid drugs (cDMARDs) (prednisolone, sulfasalazine, leflunomide, hydroxychloroquine);

methotrexate plus prednisolone; and methotrexate plus methylprednisolone. We found no RCTs comparing infliximab plus methotrexate with methotrexate monotherapy in treatment-naïve early rheumatoid arthritis.

Infliximab plus methotrexate versus methotrexate plus glucocorticoid:

We found one RCT [52] that met our inclusion criteria. This study was un-blinded after 26 weeks; therefore, we were only able to include the 26-week data in this update. We also found a comparison of infliximab plus combination synthetic cDMARDs (csDMARDs) with placebo plus combination csDMARDs in treatment-naïve early rheumatoid arthritis; [53] please see the Comment section, p 31 for more information on this study.

Symptom severity (joint damage)

Infliximab plus methotrexate compared with methotrexate plus glucocorticoid Infliximab plus methotrexate seems to have a similar effect to methylprednisolone plus methotrexate in terms of mean change in joint damage (radiological) at 26 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (joint damage)					
[52] RCT	112 adults with RA (ARA 1987 criteria) with DAS44 >2.4 and disease duration <12 months (median 1.2 months), 100% csDMARD and bDMARD naïve, no GC 1 month prior to baseline	**Mean change in modified total Sharp score (mTSS) , 26 weeks** 0.83 with infliximab plus methotrexate 1.52 with iv GC plus methotrexate 112 people in this analysis (n = 55 with infliximab plus methotrexate; n = 57 with GC plus methotrexate)	Adjusted Difference = –0.59 95%CI –1.70 to +0.52 P = 0.291	⟷	Not significant

Symptom severity (clinical symptoms)

Infliximab plus methotrexate compared with methotrexate plus glucocorticoid Infliximab plus methotrexate seems to have a similar effective to methylprednisolone plus methotrexate in terms of the clinical symptom severity (proportion achieving ACR50) at 26 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (clinical symptoms)					
[52] RCT	112 adults with RA (ARA 1987 criteria) with DAS44 >2.4 and disease duration <12 months (median 1.2 months), 100% csDMARD and bDMARD naïve, no GC 1 month prior to baseline	**Proportion achieving ACR50 , 26 weeks** 54% with infliximab plus methotrexate 55% with GC plus methotrexate 112 people in this analysis (n = 55 with infliximab plus methotrexate; n = 57 with GC plus methotrexate)	Adjusted OR = 0.95 95% CI 0.45 to 2.03 P = 0.9	⟷	Not significant

Symptom severity (function)

Infliximab plus methotrexate compared with methotrexate plus glucocorticoid Infliximab plus methotrexate seems to have a similar effect to methylprednisolone plus methotrexate in terms of the functional symptom severity (mean change in HAQ-DI) at 26 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (function)					
[52]	112 adults with RA (ARA 1987 criteria) with DAS44 >2.4 and disease duration <12 months (median 1.2 months), 100% cs-DMARD and bDMARD naïve, no GC 1 month prior to baseline	**Mean change in HAQ-DI , 26 weeks** –0.70 with infliximab plus methotrexate –0.61 with GC plus methotrexate 112 people in this analysis (n = 55 with infliximab plus methotrexate; n = 57 with GC plus methotrexate)	Adjusted OR = –0.05 95% CI –0.23 to +0.13 P = 0.57	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawals due to adverse events					
[52] RCT	112 adults with RA (ARA 1987 criteria) with DAS44 >2.4 and disease duration <12 months (median 1.2 months), 100% cs-DMARD and bDMARD naïve, no GC 1 month prior to baseline	**Proportion of withdrawals due to adverse events** 5/55 (9%) with infliximab plus methotrexate 2/57 (4%) with GC plus methotrexate			
Total reported adverse events					
[52] RCT	112 adults with RA (ACR 1987 criteria) with DAS44 >2.4 and disease duration <12 months (median 1.2 months), 100% cs-DMARD and bDMARD naïve, no GC 1 month prior to baseline	**Proportion of total adverse events** 54/55 (98%) with infliximab plus methotrexate 54/57 (95%) with GC plus methotrexate See Further information on studies			

Further information on studies

[52] The IDEA study aimed to assess the efficacy of infliximab as induction therapy in early rheumatoid arthritis. It compared infliximab plus methotrexate with intravenous glucocorticoid (GC) plus methotrexate. The infliximab group received infliximab 3 mg/kg intravenously at weeks 0, 2, 6, 14, and 22. The GC group received intravenous methylprednisolone 250 mg at week 0 and placebo infusions at weeks 2, 6, 14, and 22. Both groups received methotrexate 10 mg weekly, escalated to 20 mg or the maximum tolerated dose by week 6. The study was unblinded at 26 weeks. Therefore, we have only included the 26-week data. The primary outcome was the change in modified total Sharp score (mTSS) at week 50. However, mTSS, ACR50, and mean change in HAQ-DI at 26 weeks were also measured. There was no significant difference between the groups in the mean change in mTSS, the proportion achieving ACR50, and mean change in HAQ-DI at 26 weeks. The proportion of withdrawals due to adverse events was higher in the infliximab group, but there was no significant difference between the groups in the proportions suffering adverse events. One death was observed in the infliximab group during the study.

Comment: One study reports the 2-year results from the NEO-RACo study, [53] which aimed to establish whether addition of infliximab for the first 6 months of treatment would increase the frequency of remission and reduce radiographic progression. Therefore, all patients were treated with the standard intensified FIN-RACo regimen (i.e., methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone) on entry into the study. On weeks 4, 6, 10, 18, and 26 either infliximab 3 mg/kg iv or placebo iv was administered to the patients in the infliximab or placebo groups. According to the intensified FIN-RACo regimen, methotrexate was started at 10 mg/week and increased up to 25 mg/week by week 14. Sulfasalazine was escalated up to a maximum tolerated dose of 1–2 g/day by week 2. Hydroxychloroquine was 35 mg/kg/week. Participants had no oral GC 6 months prior or intra-articular GC 30 days prior to baseline. During the study, prednisolone was used at a fixed dose of 7.5 mg/day. Infliximab and placebo were discontinued after week 26, but the randomisation was maintained for 2 years. The co-primary endpoints were ACR remission and radiographic progression at 24 months. ACR50 and HAQ-DI were secondary endpoints measured at 6 months, 1 year, and 2 years, while radiographic progression was only measured at the 24-month time point. The study authors kindly provided the authors of this overview with the ACR50 and HAQ-DI data at 6 months and 1 year. At 2 years, there was significantly less radiographic progression, measured by mean change in modified total Sharp score (mTSS), in the group who received 6 months' induction with infliximab in addition to the intensified FIN-RACo regimen, compared with placebo plus intensified FIN-RACo regimen (–0.2 with infliximab plus FIN-RACo *v* 1.4 with placebo plus FIN-RACo; P = 0.0058; 91 people in this analysis). There was a higher proportion achieving ACR50 in the arm, including infliximab compared with placebo at 6 months, 1 year, and 2 years, but the difference was not statistically significant (6 months: 96% with infliximab plus FIN-RACo *v* 94% with placebo plus FIN-RACo, P = 0.0512; 1 year: 94% with infliximab plus FIN-RACo *v* 90% with placebo plus FIN-RACo, P = 0.463; 2 years: 96% with infliximab plus FIN-RACo *v* 92% with placebo plus FIN-RACo, P = 0.44). The same was true of effect on functional symptoms: i.e., lower mean HAQ-DI scores in the arm, including infliximab versus placebo at 6 months, 1 year, and 2 years, but not significantly different (6 months: 0.06 with infliximab plus FIN-RACo *v* 0.11 with placebo plus FIN-RACo; 1 year: 0.10 with infliximab plus FIN-RACo *v* 0.14 with placebo plus FIN-RACo; 2 years: 0.13 with infliximab plus FIN-RACo *v* 0.17 with placebo plus FIN-RACo). While 4% of patients in the infliximab group withdrew due to adverse events (1 death), there were no withdrawals due to adverse events in the placebo group. The frequency of all adverse events (45/50 [90%] with infliximab plus FIN-RACo *v* 47/49 [96%] with placebo plus FIN-RACo at 2 years) and of serious adverse events (3/50 [6%] with infliximab plus FIN-RACo *v* 4/49 [8%] with placebo plus FIN-RACo at 2 years) were similar between the groups.

Another RCT [54] compared infliximab plus methotrexate with placebo plus methotrexate in early rheumatoid arthritis. This study included 1004 patients (after randomisation and efficacy analysis), whose mean disease duration was 0.8 to 0.9 years. One third of patients had had previous csDMARDs. Therefore, 685 of the 1004 patients fulfilled the inclusion criteria for the present overview. One sixth remained on oral GCs (10 mg/day or less of prednisolone or equivalent). The three arms of the study were infliximab 3 mg/kg in combination with methotrexate, infliximab 6 mg/kg in combination with methotrexate, and placebo in combination with methotrexate. Infliximab or placebo infusions were given at weeks 0, 2, and 6 and every 8 weeks thereafter through to week 46. Methotrexate was started at 7.5 mg/week, and escalated to 15 mg by week 4 and 20 mg by week 8. At 54 weeks, treatment with infliximab 6 mg/kg plus methotrexate and infliximab 3 mg/kg plus methotrexate was significantly better than methotrexate monotherapy at achieving ACR50 (50% *v* 46% *v* 32%, respectively; P <0.001for each infliximab group *v* methotrexate monotherapy). The same significant trend was observed for ACR20, 70, and 90. While a significant proportion of patients in the infliximab 6 mg/kg group achieved DAS28 remission compared with the methotrexate monotherapy group (P <0.001), the difference in proportion was not significant between the infliximab 3 mg/kg group and the methotrexate monotherapy group. There was less radiographic progression in the infliximab 6 mg/kg group (mean change in mTSS 0.5 *v* 3.7; P <0.001) and the infliximab 3 mg/kg group (mean change in mTSS 0.4 *v* 3.7; P <0.001) compared with methotrexate monotherapy. Significantly more patients in the infliximab 6 mg/kg and 3 mg/kg group improved their HAQ-DI compared with the placebo group (P = 0.004 and P = 0.003, respectively).

Withdrawals due to adverse effects and proportion suffering serious adverse events were more frequent in the infliximab 6 mg/kg group and infliximab 3 mg/kg group compared with methotrexate monotherapy (withdrawals: 9.6% *v* 9.5% *v* 3.2%, respectively; serious adverse events: 14% *v* 14% *v* 11%, respectively). Four deaths were observed during the study: two in the methotrexate monotherapy group and one each in the infliximab 6 mg/kg and infliximab 3 mg/kg groups.

The BeSt study [55] compared four treatment strategies for early rheumatoid arthritis. Disease duration was less than 2 years, and only 43 of the 508 (9%) people included in the study had had previous antimalarials. Therefore, 465/508 people would have met the inclusion criteria for the

present overview. Group 1 received sequential monotherapy (methotrexate 15 mg/week, increased to 25–30 mg/week if DAS44 >2.4). Group 2 received step-up combination therapy (starting with methotrexate 15 mg/week, increased to 25–30 mg if DAS44 >2.4; if disease was still persistent, sulfasalazine followed by hydroxychloroquine and then by prednisolone was added in). Group 3 received initial combination therapy with prednisone (methotrexate 7.5 mg/week, sulfasalazine 2 g/day, and 60 mg prednisone tapered over 7 weeks to 7.5 mg/day). Group 4 received a combination of methotrexate and infliximab (methotrexate 25-30 mg/week with 3 mg/kg of infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter). All patients were reviewed at 3-monthly intervals, and if DAS44 was more than 2.4, the treatment was changed according to pre-set protocols for each group.

The results demonstrated a more rapid improvement in D-HAQ (Danish version of HAQ-DI) in groups 3 and 4 at 1 year compared with groups 1 and 2 (P <0.05 for groups 1 and 2 *v* groups 3 and 4). Groups 3 and 4 were also superior at maintaining less radiographic progression measure by mTSS (P <0.05 for groups 1 and 2 *v* groups 3 and 4). More patients in groups 3 and 4 achieved DAS44 remission than in groups 1 and 2 (38% in group 4 *v* 37% in group 3 *v* 35% in group 2 *v* 35% in group 1; the values were calculated by us from the published graph). Fewer patients in groups 3 and 4 required treatment escalation compared to groups 1 and 2. There is better functional improvement and less radiographic progression in group 4 compared with group 2. These findings are consistent with subsequent findings by the first study cited in this section. [53]

Though not formally assessed in the original publication, there was no significant difference between the outcomes of groups 3 and 4. Therefore, adding sulfasalazine and a tapered course of high-dose prednisone to methotrexate yielded similar effects to adding infliximab to methotrexate in the treatment of early rheumatoid arthritis. This finding is consistent with the subsequent findings of the IDEA study. [52]

Importantly, 78% of patients in group 3 were able to discontinue prednisolone because of sustained DAS44 less than 2.4, and 50% of patients in group 4 were able to discontinue infliximab due to sustained DAS44 under 2.4 by the end of 1 year of treatment.

There was no significant difference between the treatment groups in the proportion of patients experiencing all adverse effects (P = 0.367) or serious adverse effects (P = 0.438).

Clinical guide
Any benefit of infliximab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis must be weighed against the increased risk of adverse effects.

OPTION RITUXIMAB PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found insufficient direct evidence from RCTs to support the use of rituximab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Rituximab plus methotrexate:

We found no RCTs that met our inclusion criteria,but we found one RCT that included treatment-naïve patients within each arm of the study (see Comment section). The results on the treatment-naïve patients have not been published separately.

Comment: The three-armed IMAGE trial [56] compared rituximab 500 mg in combination with methotrexate, with rituximab 1000 mg in combination with methotrexate, and with placebo in combination with methotrexate. An intravenous infusion of rituximab or placebo was administered on days 1 and 15, together with methylprednisolone 100 mg. Oral methotrexate was started at 7.5 mg/week and escalated up to 20 mg/week by week 8 in all patients. A repeat course of rituximab or placebo was allowed from week 24.

The mean disease duration in the 748 included patients was 0.91 years. One third of patients had received previous conventional synthetic disease-modifying anti-rheumatoid drugs (csDMARDs). Therefore, 524/748 (70%) were treatment naïve and would have met the inclusion criteria for this overview. In addition, 46% received concomitant GCs. A total of 80% of patients received a second course of rituximab or placebo by week 30. A higher proportion treated with methotrexate monotherapy received a second course compared with the rituximab 500-mg and rituximab 1000-mg groups (44% *v* 37% *v* 36%, respectively).

The primary end point was change in modified total Sharp score (mTSS) from baseline to week 52. The rituximab 1000-mg group showed a significant reduction in radiographic progression compared with methotrexate monotherapy (mean change in mTSS 0.0359 *v* 1.079; P = 0.0004). While the rituximab 500-mg group also showed greater reduction in radiographic progression compared with methotrexate monotherapy, this was not statistically significant (P = 0.0369). A significantly greater proportion in the rituximab 1000-mg and rituximab 500-mg groups achieved ACR50 compared with the methotrexate monotherapy group (65% *v* 59% *v* 42%; P <0.0001 for each rituximab group compared with methotrexate monotherapy). The same trend was observed for mean change in HAQ-DI (–0.916 *v* –0.905 *v* –0.628; P <0.0001 for each rituximab group compared with methotrexate monotherapy).

Withdrawal due to adverse events was highest among the methotrexate monotherapy group compared with the rituximab 500-mg and rituximab 1000-mg groups (2% *v* 1% *v* 1%, respectively). Adverse events were reported in similar proportions in all three groups (81%, 76%, and 79%, respectively). However, the methotrexate monotherapy groups had a higher proportion of serious infections (5%) compared with either rituximab group (2% in rituximab 500 mg, 3% in rituximab 1000 mg). One death due to infection was observed in the methotrexate monotherapy group.

Clinical guide
There is insufficient evidence to support the use of rituximab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

OPTION TOCILIZUMAB PLUS METHOTREXATE New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- We found insufficient direct evidence from RCTs to support the use of tocilizumab plus methotrexate as a first-line treatment in early rheumatoid arthritis.

Benefits and harms

Tocilizumab plus methotrexate:

We found no RCTs that met our inclusion criteria, but we found one RCT that included treatment-naïve patients within each arm of the study (see Comment section for Tocilizumab monotherapy, p 20). The results on the treatment-naïve patients have not been published separately.

Comment: For information on the RCT, including treatment-naïve patients given tocilizumab, [44] please see the Comment section for Tocilizumab monotherapy, p 20 .

Clinical guide
There is insufficient evidence to support the use of tocilizumab in combination with methotrexate as a first-line treatment in early rheumatoid arthritis.

QUESTION **What are the effects of glucocorticoids in combination with methotrexate or with other csDMARDs versus methotrexate or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)?**

OPTION **GLUCOCORTICOIDS PLUS METHOTREXATE OR OTHER CSDMARD (OR COMBINATION OF CSDMARDS) VERSUS METHOTREXATE OR OTHER CSDMARD (OR COMBINATION OF CSDMARDS)** New

- For GRADE evaluation of interventions for Rheumatoid arthritis: previously untreated early disease, see table, p 56 .
- The addition of glucocorticoids (either as low dose or initially in high dose rapidly reducing to low dose) to methotrexate or other conventional synthetic disease-modifying anti-rheumatoid drug (csDMARDs) has a beneficial effect on reducing the rate of joint damage over 2 years, and reduces symptoms and improves function in the first 6 to 12 months of treatment.
- Adverse events in the included RCTs were generally not increased in the treatment arm, including glucocorticoids. In some studies, there were fewer adverse events in the glucocorticoid arm.
- The relative safety of glucocorticoids concurs with the report of a EULAR Task Force on recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. [57]

Benefits and harms

Glucocorticoids plus methotrexate or other csDMARD (or combination of csDMARDs) versus methotrexate or other csDMARD (or combination of csDMARDs):

We found six systematic reviews. One review [58] was limited to short-term effects (recorded within the first weeks of treatment and does not contribute to the present overview. From the remainder [27] [29] [59] [60] [61] (last search date January 2013) we identified 12 RCTs, [55] [62] [63] [64] [65] [66] [67] [68] [69] [70] [71] [72] that met our inclusion criteria, and one follow-up report. [73] We found no subsequent RCTs meeting the inclusion criteria of this overview. We have divided the following reporting into two sections: the first compares glucocorticoids plus methotrexate (with or without other csDMARDs) with methotrexate (with or without other csDMARDs); the second compares glucocorticoids plus other csDMARDs (or combination of csDMARDs) with other csDMARDs (or combination of csDMARDs). The RCTs in this second section either have not included methotrexate as the comparator csDMARD under evaluation or they have described the csDMARD intervention as 'any' and left it up to the discretion of the investigator as to which csDMARD is chosen as most appropriate for use.

Glucocorticoids plus methotrexate (with or without other csDMARDs) versus methotrexate (with or without other csDMARDs):

We found seven RCTs for this comparison. Five RCTs contributed to assessment of the disease process either by radiographs [55] [62] [63] [64] or ultrasound. [65] We have included the reporting from one systematic review [60] on the data from the first RCT. [62] Six RCTs reported clinical overall symptoms by a method meeting the inclusion criteria for this overview. [55] [63] [64] [65] [66] [67] Five RCTs reported measuring functional outcomes by a method meeting the inclusion criteria for this overview. However, three of these did not report the outcome in the results section. [63] [65] [66] We have included data from the other two RCTs for this outcome. [55] [64]

Symptom severity (joint damage)

Glucocorticoids plus methotrexate (with or without other csDMARDs) compared with methotrexate (with or without other csDMARDs) The addition of glucocorticoid to methotrexate (with or without another csDMARD) seems more effective than methotrexate (with or without other csDMARDs) at reducing progression of joint damage (radiological or ultrasound assessment) in people with rheumatoid arthritis who have not previously received DMARD therapy (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity: joint damage (radiological)					
[62] RCT	40 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean change in x-ray damage score (erosions measured by Larsen score and expressed as a proportion of maximum score) , 1 year** 4.93 with methotrexate	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [60] Data from 1 RCT	3.43 with methotrexate and prednisone See Further information on studies			
[55] RCT **4-armed trial**	508 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs other than anti-malarials	**Mean change in x-ray damage score (modified total Sharp score [mTSS]) , 1 year** 7.1 with methotrexate 2.0 with methotrexate plus sulfasalazine plus hydroxychloroquine plus prednisone (step-up combination therapy) 250 people in this analysis Patients could be treated with additional csDMARDs or biologically original DMARDs (boDMARDs) if their symptoms were persistent after 9 months The remaining 2 arms evaluated methotrexate plus sulfasalazine and initial combination therapy with prednisone, or methotrexate plus infliximab (see Further information on studies for more detail on the treatment arms and methods)	Not reported for pairwise comparison P <0.001 (among all 4 groups)		
[63] RCT **4-armed trial**	467 people with early active rheumatoid arthritis, 86% of whom had not been treated with disease-modifying anti-rheumatic drugs	**Mean change in x-ray damage score (Larsen score) , 2 years** 7.41 with methotrexate 4.70 with methotrexate plus prednisolone 188 people in this analysis The remaining 2 arms evaluated methotrexate plus ciclosporin and methotrexate plus ciclosporin plus prednisolone (see Further information on studies)	P = 0.008 (stratified factorial analysis)	○○○	methotrexate plus prednisolone
[63] RCT **4-armed trial**	467 people with early active rheumatoid arthritis, 86% of whom had not been treated with disease-modifying anti-rheumatic drugs	**Mean change in x-ray damage score (Larsen score) , 2 years** 4.53 with methotrexate plus ciclosporin 2.99 with methotrexate plus ciclosporin plus prednisolone 191 people in this analysis The remaining 2 arms evaluated methotrexate and methotrexate plus prednisolone (see Further information on studies)	P = 0.003 (stratified factorial analysis)	○○○	methotrexate plus ciclosporin plus prednisolone
[64] RCT	236 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Median (range) change in x-ray damage score (mTSS score) , 2 years** 0 (0 to 2) with methotrexate plus placebo 0 (0 to 0) with methotrexate plus prednisolone A 'tight control' treatment strategy was used Although this study was for 1 year, some patients were treated with boDMARDs after 6 months	P = 0.022	○○○	methotrexate plus prednisolone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		(see Further information on studies)			
Symptom severity (ultrasound damage)					
[65] RCT	220 patients with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion with negative power Doppler ultrasound of wrists and MCP joints (i.e., evidence for no synovitis) , 12 months** 53% with methotrexate 70% with methotrexate plus prednisone 186 people in this analysis A 'tight control' treatment strategy was used Although this study was for 1 year, some patients were treated with boDMARDs after 8 months (see Further information on studies)	RR 1.31 95% CI 1.04 to 1.64 P = 0.04	●○○	methotrexate plus prednisone

Symptom severity (clinical symptoms)

Glucocorticoids plus methotrexate (with or without other csDMARDs) compared with methotrexate (with or without other csDMARDs) The addition of glucocorticoid to methotrexate (with or without another csDMARD) may be more effective than methotrexate (with or without other csDMARDs) at increasing the proportion of people with clinical symptom improvement at 6 to 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (clinical symptoms)					
[55] RCT **4-armed trial**	508 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs other than antimalarials	**Proportion showing improvement (ACR20 response) , 6 months** 48% with methotrexate 70% with methotrexate plus sulfasalazine plus hydroxychloroquine plus prednisone (step-up combination therapy) Absolute results reported graphically 250 people in this analysis The percentages have been extracted by the contributors of this overview from the graphical data: "Clinical improvement, as defined by the ACR response criteria, was reached earlier and by more patients in group 3 (with methotrexate plus sulfasalazine plus prednisolone) than in group 1 (with methotrexate)" The remaining 2 arms evaluated methotrexate plus sulfasalazine and initial combination therapy with prednisone, or methotrexate plus infliximab Patients could be treated with additional csDMARDs or boDMARDs if their symptoms were persistent after 9 months (see Further information on studies)	P = 0.004 P value calculated by the contributors of this overview	○○○	methotrexate plus sulfasalazine plus prednisone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[63] RCT **4-armed trial**	467 people with early active rheumatoid arthritis, 86% of whom had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (DAS28 remission) , 6 months** 9% with methotrexate 36% with methotrexate plus prednisolone 188 people in this analysis The remaining 2 arms evaluated methotrexate plus ciclosporin and methotrexate plus ciclosporin plus prednisolone (see Further information on studies)			
[63] RCT **4-armed trial**	467 people with early active rheumatoid arthritis, 86% of whom had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (DAS28 remission) , 6 months** 14% with methotrexate plus ciclosporin 31% with methotrexate plus ciclosporin plus prednisolone 191 people in this analysis The remaining 2 arms evaluated methotrexate and methotrexate plus prednisolone (see Further information on studies)	P = 0.0018	○○○	methotrexate plus ciclosporin plus prednisolone
[66] RCT	210 patients with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (DAS28 remission) , 6 months** 16% with methotrexate 26% with methotrexate plus prednisone Absolute numbers not reported The study used a 'tight control' policy, increasing treatment if patients' symptoms were above a standard severity at each visit (see Further information on studies)	P = 0.082	⟷	Not significant
[67] RCT **4-armed trial**	141 patients with rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs (implied)	**Proportion showing improvement (DAS28 remission) , 6 months** 15% with methotrexate 33% with methotrexate plus prednisone Absolute numbers not reported Data have been extracted from an abstract only The remaining arms evaluated methotrexate plus iv methylprednisolone and leflunomide (see Further information on studies)	P = 0.004 P value calculated by the contributors of this overview	○○○	methotrexate plus prednisone
[64]	236 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (ACR50) , 6 months** 26% with methotrexate plus placebo 48% with methotrexate plus prednisolone Results for 6 months provided by the authors of the trial at the re-	P = 0.0005	○○○	methotrexate plus prednisolone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		quest of the contributors of this overview A 'tight control' treatment strategy was used. (see Further information on studies)			
[65]	220 patients with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion showing improvement (DAS28 remission) , 12 months** 28% with methotrexate 45% with methotrexate plus prednisone 186 people in this analysis A 'tight control' treatment strategy was used Although this study was for 1 year, some patients were treated with boDMARDs after 8 months (see Further information on studies)	P = 0.02	○○○	methotrexate plus prednisone

Symptom severity (function)

Glucocorticoids plus methotrexate (with or without other csDMARDs) compared with methotrexate (with or without other csDMARDs) The addition of glucocorticoid to methotrexate (with or without another csDMARD) may be more effective than methotrexate (with or without other csDMARDs) at improving functional symptom scores (HAQ) at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (function)					
[55] RCT **4-armed trial**	508 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs other than antimalarials	**Mean disability score (HAQ) , 6 months** 0.9 with methotrexate 0.5 with methotrexate plus sulfasalazine plus prednisone (step-up combination therapy) 250 people in this analysis The remaining 2 arms evaluated methotrexate plus sulfasalazine and initial combination therapy with prednisone, or methotrexate plus infliximab See Further information on studies for details on treatment arms and methods	Not reported for pairwise comparison P <0.001 among all 4 groups		
[64] RCT	236 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean disability score (HAQ) , 6 months** 0.72 with methotrexate plus placebo 0.47 with methotrexate plus prednisolone Results for 6 months provided by the authors of the trial at the request of the contributors of this overview A 'tight control' treatment strategy was used	P = 0.001	○○○	methotrexate plus prednisolone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawals due to adverse effects					
[55] RCT **4-armed trial**	508 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs other than anti-malarials	**Proportion of patients withdrawn due to adverse effects** 0 with methotrexate 0 with methotrexate plus sulfasalazine plus prednisone Patients could be treated with additional csDMARDs or boDMARDs if their symptoms were persistent after 9 months (see Further information on studies)			
[63] RCT **4-armed trial**	467 people with early active rheumatoid arthritis, 86% of whom had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients withdrawn due to adverse effects** 8/117 (7%) with methotrexate 14/115 (12%) with methotrexate plus prednisolone 9/119 (8%) with methotrexate plus ciclosporin 23/116 (20%) with methotrexate plus ciclosporin plus prednisolone See Further information on studies			
[64] RCT	236 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients withdrawn due to adverse effects** 20/119 (17%) with methotrexate plus placebo 16/117 (14%) with methotrexate plus prednisolone A 'tight control' treatment strategy was used Although this study was for 1 year, some patients were treated with boDMARDs after 6 months (see Further information on studies)			
[65] RCT	220 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients withdrawn due to adverse effects** 10/110 (9%) with methotrexate 6/110 (5%) with methotrexate plus glucocorticoids A 'tight control' treatment strategy was used Although this study was for 1 year, some patients were treated with boDMARDs after 9 months (see Further information on studies)			
Total reported adverse effects					
[55] RCT **4-armed trial**	508 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with 1 or more adverse effect** 54/126 (43%) with methotrexate 49/133 (37%) with methotrexate plus sulfasalazine plus prednisone	P = 0.323 P value calculated by the authors of this overview	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	other than anti-malarials	Patients could be treated with additional csDMARDs or boDMARDs if their symptoms were persistent after 9 months (see Further information on studies)			
[63] RCT **4-armed trial**	467 people with early active rheumatoid arthritis, 86% of whom had not been treated with disease-modifying anti-rheumatic drugs	**Common adverse events (occurring in >5% of cases)/number of patients in treatment group** 0.96 (112/117) with methotrexate 1.21 (139/115) with methotrexate plus prednisolone 1.56 (186/119) with methotrexate plus ciclosporin 1.52 (176/116) with methotrexate plus ciclosporin plus prednisolone See Further information on studies			
[64] RCT	236 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with 1 or more adverse effect** 94/119 (79%) with methotrexate plus placebo 86/117 (74%) with methotrexate plus prednisolone A 'tight control' treatment strategy was used Although this study was for 1 year, some patients were treated with boDMARDs after 6 months (see Further information on studies)			

Glucocorticoids plus other csDMARDS (or combination of csDMARDs) versus other csDMARDS (or combination of csDMARDs):

For this second comparison, we refer to 'other csDMARDs'. The RCTs in this comparison either have not included methotrexate as the comparator csDMARD under evaluation, or else they have described the csDMARD intervention as 'any' and left it up to the discretion of the investigator as to which csDMARD is chosen as most appropriate for use. We have also included one further RCT where the csDMARD intervention was left as a choice between im gold or methotrexate. We found five RCTs and one follow-up report. Five RCTs contributed to assessment of the disease process by radiographs [68] (data relating to DMARD-naïve patients were extracted by the authors for this overview). [69] [70] [71] [72] The follow-up report [73] served to corroborate the original findings of one of the RCTs [68] and has been included in the Comment section below. All five RCTs reported clinical overall symptoms by a method we could use in this overview. [68] [69] [70] [71] [72] Four of the RCTs reported measuring functional outcomes by a method we could use in this overview. [68] [69] [70] [71]

Symptom severity (joint damage)

Glucocorticoids plus other csDMARDs (or combination of csDMARDs) compared with other csDMARDS (or combination of csDMARDs) The addition of glucocorticoid to other csDMARD therapy may be more effective than other csDMARDs (or combination of csDMARDs) at reducing progression of joint damage (radiological) in people with rheumatoid arthritis who have not previously received DMARD therapy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (joint damage)					
[68] RCT	128 adults with active rheumatoid arthritis of less than 2 years' duration Subgroup analysis 78 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs (see Further information on studies regarding the population)	**Mean change in x-ray damage score (antilog of mean change in log transformed Larsen score) , over 2 years** 1.0077 with csDMARD plus placebo 0.0679 with csDMARD plus prednisolone 68 people in this analysis. The choice of DMARD was at the discretion of the investigator (see Further information on studies)	P = 0.0320	○○○	csDMARD plus prednisolone
[69] RCT	154 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs except antimalarials	**Median (range) change in x-ray damage score (modified total Sharp score [mTSS]) , 56 weeks** 6 (0 to 54) with sulfasalazine 2 (0 to 43) with sulfasalazine plus methotrexate plus prednisolone 135 people in this analysis See Further information on studies	P = 0.004	○○○	sulfasalazine plus methotrexate plus prednisolone
[70] RCT	167 people with rheumatoid arthritis symptoms <3 years (mean 12 months) who had probably not been treated with disease-modifying anti-rheumatic drugs except hydroxychloroquine	**Median (range) change in x-ray damage score (SHS score) done by 2 readers , over 2 years** 59 (8 to 213) and 10 (0 to 108) with sulfasalazine plus placebo 64 (9 to 174) and 13 (0 to 82) with sulfasalazine plus prednisolone The 2 values are the 2 separate scores measured by different readers X-rays available for 66/84 people with sulfasalazine and 64/83 people with sulfasalazine plus prednisolone The study allowed possible later additional DMARDs in both arms (see Further information on studies)	P = 0.815 and P = 0.564	⟷	Not significant
[71] RCT	250 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Median and interquartile range (IQR) change in x-ray damage score (mTSS score) , 2 years** 3.5 (0.5 to 10) with csDMARD 1.8 (0.5 to 6.0) with csDMARD plus prednisolone 225 people in this analysis (n = 117 with csDMARD; n = 108 with csDMARD plus prednisolone) Participants could take any csDMARD at the discretion of the investigator (see Further information on studies)	P = 0.019	○○○	csDMARD plus prednisolone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[72] RCT	166 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Median change in x-ray damage score (mTSS score) , 2 years** 11.4 with csDMARD plus placebo 5.3 with csDMARD plus prednisolone 142 people in this analysis Participants could take im gold or methotrexate at the discretion of the investigator (see Further information on studies)	Least squares MD 7.20 95% CI 0.93 to 13.47 P = 0.022	○○○	csDMARD plus prednisolone

Symptom severity (clinical symptoms)

Glucocorticoids plus other csDMARDs (or combination of csDMARDs) compared with other csDMARDS (or combination of csDMARDs) The addition of glucocorticoid to other csDMARDs (or combination of csDMARDS) may be more effective than other csDMARDs (or combination of csDMARDS) at reducing severity of clinical symptoms at 6 months in people with rheumatoid arthritis who have not previously received DMARD therapy. However, there was no significant difference between groups at 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (clinical symptoms)					
[68] RCT	128 adults with active rheumatoid arthritis of less than 2 years' duration Subgroup analysis 78 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs (see Further information on studies)	**Mean reduction in articular index , over 6 months** 118 with csDMARD 139 with csDMARD plus prednisolone The choice of DMARD was at the discretion of the investigator; see Further information on studies	P = 0.1757	⟷	Not significant
[69] RCT	154 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs except antimalarials	**Proportion showing improvement (ACR50 response) , 6 months** 27% with sulfasalazine 49% with sulfasalazine plus methotrexate plus prednisolone See Further information on studies	P = 0.007	○○○	sulfasalazine plus methotrexate plus prednisolone
[70] RCT	167 people with rheumatoid arthritis symptoms <3 years (mean 12 months) who had probably not been treated with disease-modifying anti-rheumatic drugs except hydroxychloroquine	**Proportion showing improvement ('modified ACR20' response) , 12 months** 39% with sulfasalazine plus placebo 53% with sulfasalazine plus prednisolone The study allowed possible later additional DMARDs in both arms (see Further information on studies)	P = 0.07	⟷	Not significant
[71] RCT	250 people with early active rheumatoid arthritis who had not been	**Proportion showing improvement (DAS28 remission) , 12 months**	P = 0.06	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	treated with disease-modifying anti-rheumatic drugs	39% with csDMARD 51% with csDMARD plus prednisolone Participants could take any csDMARD at the discretion of the investigator 248 people in this analysis (n = 130 with csDMARD; n = 118 with csDMARD plus prednisolone) There was a benefit in favour of the combination intervention at 2 years (see Further information on studies)			
[72] RCT	166 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Median reduction in Thompson (articular) index , 6 months** 81.5 with csDMARD plus placebo 116.0 with csDMARD plus prednisolone Participants could take im gold or methotrexate at the discretion of the investigator (see Further information on studies)	P = 0.029	○○○	csDMARD plus prednisolone

Symptom severity (function)

Glucocorticoids plus other csDMARDS (or combination of csDMARDs) compared with other csDMARDS (or combination of csDMARDs) The addition of glucocorticoid to other csDMARDs (or combination of csDMARDs) seems to be more effective than other csDMARDs (or combination of csDMARDs) at improving functional symptom scores (HAQ) at 6 months in people with rheumatoid arthritis who have not previously received DMARD therapy (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity (function)					
[68] RCT	128 adults with active rheumatoid arthritis of <2 years' duration Subgroup analysis 78 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs (see Further information on studies)	**Mean reduction in disability score (HAQ) , 6 months** 0.388 with csDMARD 0.571 with csDMARD plus prednisolone The choice of DMARD was at the discretion of the investigator; see Further information on studies	P = 0.6843	⟷	Not significant
[69] RCT	154 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs except antimalarials	**Mean reduction in disability score (HAQ) , 28 weeks** 0.6 with sulfasalazine 1.1 with sulfasalazine plus methotrexate plus prednisolone See Further information on studies	Mean difference 0.5 95% CI 0.3 to 0.7 P <0.0001	○○○	sulfasalazine plus methotrexate plus prednisolone
[70] RCT	167 people with rheumatoid arthritis symptoms <3 years (mean 12	**Reduction in median disability score (HAQ) , 12 months** 0.13 with sulfasalazine plus placebo	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	months) who had probably not been treated with disease-modifying anti-rheumatic drugs except hydroxychloroquine	0.37 with sulfasalazine plus prednisolone The study allowed possible later additional DMARDs in both arms (see Further information on studies)			
[71] RCT	250 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Mean disability score (HAQ) , 6 months** 0.72 with csDMARD 0.42 with csDMARD plus prednisolone Absolute results reported graphically Data extracted from the graph by the contributors of this overview Patients could take any csDMARD at the discretion of the investigator (see Further information on studies)	P = 0.0005	○○○	csDMARD plus prednisolone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawals due to adverse effects					
[68] RCT	128 adults with active rheumatoid arthritis of <2 years' duration Subgroup analysis 78 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients withdrawn due to adverse effects** 4/67 (6%) with csDMARD 1/61 (2%) with csDMARD plus prednisolone			
[69] RCT	154 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs except antimalarials	**Proportion of patients withdrawn due to adverse effects** 7/79 (9%) with sulfasalazine 2/76 (3%) with sulfasalazine plus methotrexate plus glucocorticoids See Further information on studies			
[70] RCT	167 people with rheumatoid arthritis symptoms <3 years (mean 12 months) who had probably not been treated with disease-modifying anti-rheumatic drugs except hydroxychloroquine	**Proportion of patients withdrawn due to adverse effects** 23/83 (28%) with sulfasalazine plus placebo 17/84 (20%) with sulfasalazine plus prednisolone The study allowed possible later additional DMARDs in both arms (see Further information on studies)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[72] RCT	166 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients withdrawn due to adverse effects , 2 years** 12/86 (14%) with csDMARD plus placebo 10/80 (13%) with csDMARD plus prednisolone Participants could take im gold or methotrexate at the discretion of the investigator (see Further information on studies)			
Total reported adverse effects					
[60] RCT	128 adults with active rheumatoid arthritis of less than 2 years' duration Subgroup analysis 78 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with adverse effects** with csDMARD with csDMARD plus prednisolone Reported as 'no difference between groups'			
[69] RCT	154 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs except antimalarials	**Number of adverse effects** 41 with sulfasalazine 52 with sulfasalazine plus methotrexate plus prednisolone See Further information on studies			
[71] RCT	250 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Number of patients with permanent or temporary withdrawal of treatment , 2 years** 24 with csDMARD 26 with csDMARD plus prednisolone Participants could take any csDMARD at the discretion of the investigator (see Further information on studies)			
[72] RCT	166 people with early active rheumatoid arthritis who had not been treated with disease-modifying anti-rheumatic drugs	**Proportion of patients with any adverse effects , 2 years** 74% with csDMARD plus placebo 71% with csDMARD plus prednisolone 189 people in this analysis (n = 96 with csDMARD plus placebo; n = 93 with csDMARD plus prednisolone) Participants could take im gold or methotrexate at the discretion of the investigator (see Further information on studies)			

Further information on studies

[62] In this study methotrexate 7.5–10 mg per week was compared with methotrexate 7.5–10 mg/week plus up to 10 mg/day of oral prednisone. It is published in Russian; the original paper could not be located electronically, but changes in Larsen erosion score were reported in an earlier systematic review, [60] following appropriate translation, and are included here directly from that review. An abstract is now available [62] that describes the development of new erosions and achievement of ACR70 and quotes them as significantly different between treatment groups, but does not provide the numerical values. The mean change in damage (erosions) showed a non-significant benefit in favour of combination therapy at 1 year. The authors also report that the number of new erosions was "much fewer" in the combination arm (P <0.05), a benefit in favour of combination therapy, but do not provide the numerical data. ACR70 was the reported clinical outcome that most closely resembled ACR50, and the authors report the proportion of patients to be more in favour of combination therapy (P <0.05) at 1 year. HAQ was not reported. Adverse events were not reported.

[55] This RCT (the BeSt study) compared four treatment strategies for early rheumatoid arthritis. Disease duration was less than 2 years, and only 43 of the 508 (9%) patients included in the study had had previous antimalarials. Therefore, 465/508 patients would have met the inclusion criteria for the present overview. Group 1 received sequential monotherapy (methotrexate 15 mg/week, increased to 25–30 mg/week if DAS44 >2.4). Group 2 received step-up combination therapy (starting with methotrexate 15 mg/week, increased to 25–30 mg if DAS44 >2.4; if disease was still persistent, sulfasalazine followed by hydroxychloroquine and then by prednisolone was added in). Group 3 received initial combination therapy with prednisone (methotrexate 7.5 mg/week, sulfasalazine 2 g/day, and 60 mg prednisone tapered over 7 weeks to 7.5 mg/day). Group 4 received a combination of methotrexate and infliximab (methotrexate 25–30 mg/week with 3 mg/kg of infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter). All patients were reviewed at 3-monthly intervals, and if DAS44 was more than 2.4, the treatment was changed according to pre-set protocols for each group.

[55] In this option, we have focused on two treatment arms only. Methotrexate 15 mg/week (increasing or replaced if DAS44 >2.4) was compared with methotrexate 15 mg/week (increasing or replaced if DAS44 >2.4) plus sulfasalazine 2000 mg/day plus hydroxychloroquine 400 mg/day plus prednisone 60 mg/day (reducing to 7.5 mg/day after 7 weeks); therefore, the additional sulfasalazine could be contributing. Further, patients could be treated with additional csDMARDs or boDMARDs if their symptoms were persistent after 9 months. From 9 to 12 months 30% of the methotrexate group but less than 10% of combination group were treated with boDMARDs. Because combination csDMARDs have relatively little (if any) advantage over methotrexate alone, and because the additional treatments were received in a way that biases against the outcome reported, we included this study in full. The mean change in total damage score showed a benefit in favour of combination therapy at 1 year. In addition the proportion of patients showing no damage progression showed a benefit in favour of combination therapy at 1 year. ACR20 was the reported clinical outcome that most closely resembled ACR50, and there was a benefit in favour of combination therapy at 1 year. Mean HAQ score was reported and there was a benefit in favour of combination therapy at 1 year. No patient from either group withdrew due to adverse effects. The overall incidence of adverse effects showed a non-significant benefit in favour of combination therapy.

[55] Concerning the other treatment arms, the results demonstrated a more rapid improvement in D-HAQ (Danish version of HAQ-DI) in groups 3 and 4 at 1 year compared with groups 1 and 2 (P <0.05 for groups 1 and 2 *v* groups 3 and 4). Groups 3 and 4 were also superior at maintaining less radiographic progression measure by modified total Sharp score (mTSS) (P <0.05 for groups 1 and 2 *v* groups 3 and 4). More patients in groups 3 and 4 achieved DAS44 remission than in groups 1 and 2 (38% in group 4 *v* 37% in group 3 *v* 35% in group 2 *v* 35% in group 1; the values were calculated by us from the published graph). Fewer patients in groups 3 and 4 required treatment escalation compared to groups 1 and 2. There is better functional improvement and less radiographic progression in group 4 compared with group 2.

[55] Though not formally assessed in the original publication, there was no significant difference between the outcomes of groups 3 and 4. Therefore, adding sulfasalazine and a tapered course of high-dose prednisone to methotrexate yielded similar effects to adding infliximab to methotrexate in the treatment of early rheumatoid arthritis. Importantly, 78% of patients in group 3 were able to discontinue prednisolone because of sustained DAS44 less than 2.4, and 50% of patients in group 4 were able to discontinue infliximab due to sustained DAS44 less than 2.4 by the end of 1 year of treatment.

[63] In this four-armed RCT, methotrexate 7.5 mg/week increasing to 15 mg/week (group A) was compared with methotrexate 7.5 mg/week increasing to 15 mg/week plus prednisolone 60 mg/day reduced to 7.5 mg/day over 6 weeks (group B), versus methotrexate 7.5 mg/week increasing to 15 mg/week plus ciclosporin 100 mg/day increased to 3 mg/kg (group C), versus methotrexate 7.5 mg/week increasing to 15 mg/week plus ciclosporin 100 mg/day increased to 3mg/kg plus prednisolone 60 mg/day reduced to 7.5 mg/day over 6 weeks (group D). All groups continued treatment for up to 34 weeks and were then followed for 2 years. The authors present a four-way analysis, concluding that the addition of glucocorticoids is beneficial. We have included two comparisons: group A compared with group B, and group C compared with group D. This avoids counting patients more than once and provides a conservative presentation of the outcomes. Patients in the methotrexate and methotrexate plus ciclosporin groups had more adjustments to treatment, introducing a bias against the reported outcome of the study, which we, therefore, included. Change in damage score showed a benefit in favour of combination

therapy at 1 year in both comparisons. ACR50 was reported, but only to compare group A+C to groups B+D, and showed a benefit in favour of adding glucocorticoid treatment. DAS28 remission showed a benefit in favour of adding glucocorticoid treatment for group A compared with group B and for group C compared with group D. HAQ was not reported. The proportion who withdrew due to adverse effects showed a non-significant benefit against combination therapy in both comparisons. The overall incidence of adverse effects showed a non-significant benefit against combination therapy comparing group A with group B but no difference between group C and group D.

[66] In this RCT, methotrexate 10 mg/week, increasing every 2 months on tight control if needed to 20 mg/week if DAS more than 2.4 (boDMARD after 6 months if needed) ('non-P' group), was compared with methotrexate 10 mg/week, increasing every 2 months on tight control if needed to 20 mg/week if DAS greater than 2.4 (boDMARD after 6 months if needed) plus prednisone 12.5 mg/day for 2 weeks, then 6.25 mg/day ('P' group). Although this study was for 1 year, some patients were treated with boDMARDs after 6 months. Therefore, data for the first 6 months only were included. The study used a 'tight control' policy, increasing treatment if patients' symptoms were above a standard severity at each visit. Some patients, therefore, received more treatment than others. Methotrexate monotherapy patients had more such adjustments to treatment under tight control, and thus additional treatments were received in a way that biases against the outcome reported. We, therefore, included the first 6 months of this study in full. No damage score was reported. DAS28 remission (<1.6) was the reported clinical outcome that most closely resembled ACR50, and there was a non-significant benefit in favour of combination therapy at 6 months. HAQ was not reported. Adverse effects were not reported in a way that can be incorporated in this overview.

[67] This report (abstract only) is from a refereed abstract presented at a meeting of the European League Against Rheumatism (EULAR). The contributors of this overview have not been able to identify a full report, and the senior author has not replied to requests for further data. In this study methotrexate up to 20 mg/week (group 1) was compared with methotrexate up to 20 mg/week plus prednisolone 10 mg/day (group 2), methotrexate up to 20 mg/week plus one dose of iv methylprednisolone 1000 mg (group 3), and leflunomide 20 mg/day (group 4). Attainment of EULAR remission is reported and the comparison of group 1 with group 2 is included here. No damage score was reported. EULAR remission (DAS28 <1.6) was the reported clinical outcome that most closely resembled ACR50, and there was a benefit in favour of combination therapy at 3, 6, and 12 months. HAQ was not reported. Adverse effects were not reported in a way that can be incorporated in this overview.

[64] In this RCT, methotrexate 10 mg/week increasing every month on 'tight control' for poor response if needed to 30 mg/week, and boDMARD after 6 months if needed, was compared with methotrexate 10 mg/week increasing every month on tight control if needed to 30 mg/week plus prednisolone 10 mg/day, and boDMARD after 6 months if needed. Poor response was defined by a computer algorithm. Although this study was for 1 year, some patients were treated with boDMARDs after 6 months. Some patients, therefore, received more treatment than others. Methotrexate patients had more such adjustments to treatment under tight control (41% *v* 15%, P <0.01), and thus additional treatments were received in a way that biases against the outcome reported. We, therefore, included this study in full. Change in damage score showed a benefit in favour of combination therapy at 2 years. ACR50 showed a benefit in favour of combination therapy at 6 months and a non-significant benefit in favour of combination therapy at 1 year and 2 years. (Data on ACR50 responders at 6 months provided by the authors of the RCT were methotrexate plus placebo 26% and methotrexate plus prednisolone 48%; P = 0.0005.) HAQ showed a benefit in favour of combination therapy at 6 months, 1 year, and 2 years. The proportion who withdrew due to adverse effects (AE) showed a non-significant benefit in favour of combination therapy. The overall incidence of AE showed no difference between treatments. The triallists comment that, "The trial was not powered to compare adverse effects, including infection".

[65] In this RCT, methotrexate 10 mg/week, increasing every 2 months on 'tight control' for poor response (DAS28 remained >2.4) if needed to 25 mg/week, was compared with methotrexate 10 mg/week, increasing every 2 months on tight control if needed to 25 mg/week plus prednisolone 10 mg/day. This study used ultrasound to assess the joint damage in terms of synovitis. Although this study was for 1 year, some patients were treated with boDMARDs after 8 months. Some patients therefore received more treatment than others. Methotrexate patients had more such adjustments to treatment under tight control (RR 0.77, P = 0.19), and thus additional treatments were received in a way that biases against the outcome reported. We, therefore, included this study in full. The ultrasound damage score showed a benefit in favour of combination therapy at 1 year. EULAR remission (DAS28 <1.6) was the reported clinical outcome that most closely resembled ACR50, and there was a benefit in favour of combination therapy at 1 year. HAQ was not reported. The overall incidence of adverse effects was not reported.

[68] In this RCT, participants could take any csDMARD at the discretion of the investigator, but in addition took placebo or glucocorticoid tablets (prednisolone 7.5 mg/day). A minority of patients had already started csDMARD more than a few weeks before recruitment, and the data relating to the DMARD-naïve patients were extracted by the authors for this overview. Damage was measured by the change in Larsen score and by change in the proportion of erosive x-rays. For DMARD-naïve patients with available x-rays (36 for baseline to 1 year and 35 for baseline to 2 years in the prednisolone group and 34 and 33 respectively in the placebo group), progression was 0.0805 at year 1 and 0.0679 at year 2 (antilog of mean change in log transformed Larsen score) in the prednisolone group and 0.7187 and 1.0077 in the placebo group (P = 0.0691 and P = 0.0320, respectively).

The proportion of hands that had erosions at baseline, 1, and 2 years was 23.0%, 23.6%, and 27.1% in the prednisolone group and 21.4%, 42.6%, and 48.5% in the placebo group (P = 0.7807, P = 0.0742, and P = 0.0481, respectively). Thus, there was a benefit in favour of combination therapy at 1 and 2 years. Articular index was the reported clinical outcome that most closely resembled ACR50. In the DMARD-naïve prednisolone group (n = 38), this was reduced by 143 units at 3 months, 139 units at 6 months, 132 units at 1 year, and 135 units at 2 years. In the DMARD-naïve placebo group (n = 40) the equivalent changes were 56, 118, 120, and 120 units (P = 0.0014, P = 0.1757, P = 0.6843, and P = 0.6348, respectively). Thus, there was a benefit in favour of combination therapy at 3 months and a non-significant benefit in favour of combination therapy thereafter. HAQ scores in the DMARD-naïve prednisolone group were reduced by 0.48, 0.57, 0.47, and 0.41 at 3 months, 6 months, 1 year, and 2 years and the equivalent figures in the placebo group were 0.15, 0.39, 0.48, and 0.37 (P = 0.003, P = 0.6843, P = 0.9318, and P = 0.8115, respectively). Thus, there was a benefit in favour of combination therapy at 3 months. The proportion who withdrew due to adverse effects showed a non-significant benefit in favour of combination therapy, and the authors report 'no difference between groups' in the overall incidence of adverse effects.

[69] This RCT compared sulfasalazine 500 mg/day increasing to 2000 mg/day with sulfasalazine 500 mg/day increasing to 2000 mg/day plus methotrexate 7.5 mg/week (for 40 weeks, then tapered over 6 weeks) plus prednisolone 60 mg/day (then weekly reduction to 40, then 25, then 20, then 15, then 10, then 7.5 mg/day, continuing for 28 weeks then reducing over 7 weeks). Because combination csDMARDs have relatively little (if any) advantage over a single csDMARD alone, we included this study in full in the main data analysis above. Damage scores showed a benefit in favour of combination therapy at 6 months and 1 year. ACR50 showed a benefit in favour of combination therapy at 4 months and 6 months and a non-significant benefit in favour of combination therapy at 1 year. HAQ showed a benefit in favour of combination therapy at 6 months and a non-significant benefit in favour of combination therapy at 1 year. The proportion who withdrew due to adverse effects showed a non-significant benefit in favour of combination therapy. The overall incidence of adverse effects showed a non-significant benefit against combination therapy.

[73] This was a blind withdrawal of treatment for 1 year following on from a 1995 study. [68] It served to corroborate the original findings of the 1995 RCT. Following treatment termination, damage scores progressed at the same rate in both treatment groups for 1 year, but articular index and HAQ showed no changes.

[70] All the other RCTs we found included patients within 2 years of diagnosis, but this study included patients up to 3 years after the onset of symptoms; the mean time was 12 months. It is highly likely that these patients were within 2 years of diagnosis, so the study was included in full. There are reservations about the quality of the study (e.g., the results provided by the two x-ray readers differ considerably) and the study report (e.g., there are inconsistencies in the reporting of non-erosive patients). The study compared sulfasalazine 500 mg/day increasing to 40 mg/kg/day, and possibly later additional DMARDs, with sulfasalazine 500 mg/day increasing to 40 mg/kg/day, and possibly later additional DMARDs, plus prednisolone 7 mg/day, for 2 years. Damage scores showed non-significant benefits against combination therapy at 1 year and 2 years. A modified ACR20 was the reported clinical outcome that most closely resembled ACR50, and there was a non-significant benefit in favour of combination therapy at 1 year and 2 years. HAQ showed a non-significant benefit in favour of combination therapy at 1 year and 2 years. The proportion who withdrew due to adverse effects showed a non-significant benefit in favour of combination therapy. Total adverse effects were not reported.

[71] In this RCT, participants could take any csDMARD at the discretion of the investigator, but in addition took either no additional medication or prednisolone 7.5 mg/day. The study was, therefore, not blind but treatment was maintained to the same extent in both groups and the radiographic outcomes were measured blind. Therefore, it has been included in the analysis. Damage scores showed a benefit in favour of combination therapy at 1 year and 2 years. DAS28 remission was the reported clinical outcome that most closely resembled ACR50, and there was a non-significant benefit in favour of combination therapy at 1 year and a benefit in favour of combination therapy at 2 years. The HAQ showed a benefit in favour of combination therapy at 6 months, 1 year, and 2 years. Withdrawals due to adverse effects were not reported. Total adverse effects showed a non-significant benefit against combination therapy.

[72] In this RCT, participants could take im gold or methotrexate at the discretion of the investigator, but in addition took prednisolone 5 mg/day or placebo tablets. Damage scores showed a benefit in favour of combination therapy at 1 year and 2 years. Thompson (articular index) was the reported clinical outcome that most closely resembled ACR50, and there was a benefit in favour of combination therapy at 6 months and a non-significant benefit in favour of combination therapy at 1 year and 2 years. HAQ was not reported. The proportion who withdrew due to adverse effects showed a non-significant benefit in favour of combination therapy. Total adverse effects showed a non-significant benefit in favour of combination therapy.

Comment: A recommended nomenclature system for glucocorticoid (GC) treatment [74] is used as follows: the dose is either low (7.5 mg or less prednisone equivalent daily [GC-l]), medium (>7.5–30 mg prednisone equivalent daily [GC-m]), high (>30–100 mg prednisone equivalent daily [GC-h]), very high (>100 mg prednisone equivalent daily [GC-vh]), or pulse (>250 mg prednisone equivalent per

day [usually intravenously] for 1 or a few [usually <5] days [GC-p]). The route of administration is either oral (poGC), intramuscular (imGC), intravenous (ivGC), intra-articular (iaGC), or other (otherGC).

It is notable that there are a variety of GCs used in clinical practice. The relative potency of the GCs are 1 mg prednisone = 1 mg prednisolone = 5 mg cortisone = 4 mg hydrocortisone = 0.8 mg triamcinolone = 0.8 mg methylprednisolone = 0.2 mg dexamethasone = 0.2 mg betamethasone. [74] [75] [76]

Many studies reported appropriate outcomes at other time points. Many studies found a result in favour of one of the treatment arms, which did not reach statistical significance. However, consistency in such findings will suggest a positive effect, and they would be included in a formal meta-analysis. Therefore, we considered all the findings and included them in our overall assessment. Taken together, the results show a substantial and continuing beneficial effect of combination therapy with methotrexate and glucocorticoids, or other csDMARDs with glucocorticoids, on joint damage for 2 years, but a tendency for the symptom and functional benefits to reduce after 6 months. Adverse events in the included RCTs were generally not increased in the treatment arm including glucocorticoids. In some studies there were fewer adverse events in the glucocorticoid arm. The relative safety of glucocorticoids concurs with the report of a EULAR Task Force on recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. [57]

Clinical guide
The addition of glucocorticoids (either as low dose or initially in high dose rapidly reducing to low dose) to methotrexate other csDMARDS (or combination csDMARDs) has a beneficial effect on reducing the rate of joint damage over 1 to 2 years, and reduces symptoms and improves function in the first 6 to 12 months of treatment.

GLOSSARY

Larsen score Assesses radiological damage by scoring joints from 0 (normal) to 5; possible score range 0–250.

Sharp score Assesses radiological damage by measuring erosions and joint space narrowing in 44 different joints and reporting an aggregated score ranging from 0 to 448.

American College of Rheumatology (ACR) criteria Measure for assessing response; includes seven items in its core data set: swollen joint count, tender joint count, patient assessment of global status, an acute phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), health professional assessment of global status, physical function, and pain. Improvement criteria are based on improvement of at least 20% in both tender and swollen joint counts, and three of the five additional measures (ACR 20); and corresponding ACR 50, 50% improvement; and ACR 70, 70% improvement.

Disease Activity Score (DAS) A clinical index of disease activity that combines information from swollen joints, tender joints, erythrocyte sedimentation rate (ESR), and general health or global disease activity measured on a visual analogue scale.

European League Against Rheumatism (EULAR) response criteria A classification of trial participants as 'good', 'moderate', or 'non-responders' using individual change from baseline in Disease Activity Score.

Health Assessment Questionnaire (HAQ) Assesses eight functional categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. For each of these domains, patients report the amount of difficulty they have had in performing two to three specific activities in the previous week, assessing each activity on a scale from 0 (without any difficulty) to 3 (unable to do). By convention, the HAQ Disability Index (HAQ-DI) is expressed on a scale from 0 to 3 units, representing the mean of the eight domain scores. A HAQ-DI of 0 indicates no functional disability, while a HAQ-DI of 3 indicates severe functional disability.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Methotrexate plus other csDMARD therapy versus methotrexate monotherapy New option. Six systematic reviews [26] [27] [28] [29] [30] [31] and eight RCTs added. [32] [33] [34] [35] [36] [37] [38] [39] Categorised as 'unlikely to be beneficial'.

Abatacept monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Anakinra monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Certolizumab monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Infliximab monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Rituximab monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Tofacitinib monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Adalimumab monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Etanercept monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Golimumab monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Tocilizumab monotherapy New option. No evidence found. Categorised as 'unknown effectiveness'.

Abatacept plus methotrexate New option. No evidence found. Categorised as 'unknown effectiveness'.

Anakinra plus methotrexate New option. No evidence found. Categorised as 'unknown effectiveness'.

Certolizumab plus methotrexate New option. No evidence found. Categorised as 'unknown effectiveness'.

Tofacitinib plus methotrexate New option. No evidence found. Categorised as 'unknown effectiveness'.

Adalimumab plus methotrexate New option. Three RCTs added. [45] [46] [47] Categorised as 'likely to be beneficial'.

Etanercept plus methotrexate New option. One RCT added. [50] Categorised as 'likely to be beneficial'.

Golimumab plus methotrexate New option. No evidence found. Categorised as 'unknown effectiveness'.

Infliximab plus methotrexate New option. One RCT added. [52] Categorised as 'trade off between benefits and harms'.

Rituximab plus methotrexate New option. No evidence found. Categorised as 'unknown effectiveness'.

Tocilizumab plus methotrexate New option. No evidence found. Categorised as 'unknown effectiveness'.

Glucocorticoids plus methotrexate or other csDMARD (or combination of csDMARDs) versus methotrexate or other csDMARD (or combination of csDMARDs) New option. Six systematic reviews [27] [29] [58] [59] [60] [61] 12 RCTs, [55] [62] [63] [64] [65] [66] [67] [68] [69] [70] [71] [72] and one follow-up report added. [73] Categorised as 'beneficial'.

REFERENCES

1. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management. February 2009. Available at https://www.nice.org.uk/guidance/cg79 (last accessed 6 April 2016).
2. Smolen JS, van der Heijde D, Machold KP, et al. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2014;73:3–5.[PubMed]
3. van der Linden MP, le Cessie S, Raza K, et al. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis Rheum* 2010;62:3537–3546.[PubMed]
4. Möttönen T, Hannonen P, Korpela M, et al; FIN-RACo Trial Group. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002;46:894–898.[PubMed]
5. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–324.[PubMed]
6. van der Heijde DM, van 't Hof MA, van Riel PL, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;49;916–920.[PubMed]
7. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. *Arthritis Rheum* 2007;57:193–202.[PubMed]
8. Pincus T, Callahan LF, Fuchs HA, et al. Quantitative analysis of hand radiographs in rheumatoid arthritis: time course of radiographic changes, relation to joint examination measures, and comparison of different scoring methods. *J Rheumatol* 1995;22:1983–1989.[PubMed]
9. Fries JF, Spitz PW, Kraines RG,et al. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–145.[PubMed]
10. Sokka T, Kautiainen H, Pincus T, et al; QUEST-RA. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. *Arthritis Res Ther* 2010;12:R42.[PubMed]
11. Rudan I, Sidhu S, Papana A, et al; Global Health Epidemiology Reference Group (GHERG). Prevalence of rheumatoid arthritis in low- and middle-income countries: a systematic review and analysis. *J Glob Health* 2015;5:010409.[PubMed]
12. Symmons D, Turner G, Webb R, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology (Oxford)* 2002;41:793–800.[PubMed]
13. Myasoedova E, Crowson CS, Kremers HM, et al. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955-2007. *Arthritis Rheum* 2010;62:1576–1582.[PubMed]
14. Humphreys JH, Verstappen SM, Hyrich KL, et al. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from Norfolk Arthritis Register. *Ann Rheum Dis* 2013;72:1315–1320.[PubMed]
15. Klein K, Gay S. Epigenetics in rheumatoid arthritis. *Curr Opin Rheumatol* 2015;27:76–82.[PubMed]
16. Vencovský J, Machácek S, Sedová L, et al. Autoantibodies can be prognostic markers of an erosive disease in early rheumatoid arthritis. *Ann Rheum Dis* 2003;62:427–430.[PubMed]
17. Weinblatt ME, Keystone EC, Cohen MD, et al. Factors associated with radiographic progression in patients with rheumatoid arthritis who were treated with methotrexate. *J Rheumatol* 2011;38:242–246.[PubMed]
18. Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001;111:446–451.[PubMed]
19. McWilliams DF, Varughese S, Young A, et al. Work disability and state benefit claims in early rheumatoid arthritis: the ERAN cohort. *Rheumatology (Oxford)* 2014;53:473–481.[PubMed]
20. Goodson N, Marks J, Lunt M, et al. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. *Ann Rheum Dis* 2005;64:1595–1601.[PubMed]
21. Humphreys JH, Warner A, Chipping J, et al. Mortality trends in patients with early rheumatoid arthritis over 20 years: results from the Norfolk Arthritis Register. *Arthritis Care Res (Hoboken)* 2014;66:1296–1301.[PubMed]
22. Listing J, Kekow J, Manger B, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNF-alpha inhibitors and rituximab. *Ann Rheum Dis* 2015;74:415–421.[PubMed]
23. Scott DL, Pugner K, Kaarela K, et al. The links between joint damage and disability in rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39:122–132.[PubMed]
24. Kirwan JR. Links between radiological change, disability and pathology in rheumatoid arthritis. *J Rheumatol* 2001;28:893–898.[PubMed]
25. Welsin PMJ, Borm GF, van Riel P. Minimal clinically important difference in radiological progression of joint damage: a definition based on patient perspective. *J Rheumatol* 2006;33:501–507.[PubMed]
26. Katchamart W, Trudeau J, Phumethum V, et al. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying antirheumatic drugs for rheumatoid arthritis. In: The Cochrane Library, Issue 12, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2009.
27. Graudal N, Jürgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. *Arthritis Rheum* 2010;62:2852–2863.[PubMed]
28. Gaujoux-Viala C, Smolen JS, Landewé R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1004–1009.[PubMed]
29. Gaujoux-Viala C, Nam J, Ramiro S, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:510–515.[PubMed]

30. Knevel R, Schoels M, Huizinga TW, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:987–994.[PubMed]
31. Graudal N, Hubeck-Graudal T, Tarp S, et al. Effect of combination therapy on joint destruction in rheumatoid arthritis: a network meta-analysis of randomized controlled trials. *PLoS One* 2014;9:e106408.[PubMed]
32. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999;58:220–225.[PubMed]
33. Marchesoni A, Battafarano N, Arreghini M, et al. Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone. *Rheumatology (Oxford)* 2003;42:1545–1549.[PubMed]
34. Hetland ML, Stengaard-Pedersen K, Junker P, et al; CIMESTRA Study Group. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. *Arthritis Rheum* 2006;54:1401–1409.[PubMed]
35. Haagsma CJ, van Riel PL, de Jong AJ, et al. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. *Br J Rheumatol* 1997;36:1082–1088.[PubMed]
36. O'Dell JR, Elliott JR, Mallek JA, et al. Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. *Arthritis Rheum* 2006;54:621–627.[PubMed]
37. de Jong PH, Hazes JM, Barendregt PJ, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. *Ann Rheum Dis* 2013;72:72–78.[PubMed]
38. Moreland LW, O'Dell JR, Paulus HE, et al; TEAR Investigators. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the Treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum* 2012;64:2824–2835.[PubMed]
39. Verschueren P, De Cock D, Corluy L, et al. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. *Ann Rheum Dis* 2015;74:27–34.[PubMed]
40. Emery P, Burmester GR, Bykerk VP, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann Rheum Dis* 2015;74:19–26.[PubMed]
41. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.[PubMed]
42. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586–1593.[PubMed]
43. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;60:2272–2283.[PubMed]
44. Burmester G, Rigby W, van Vollenhoven RF, et al. Tocilizumab in combination therapy and monotherapy versus methotrexate in methotrexate-naïve patients with early rheumatoid arthritis: clinical and radiographic outcomes from a randomized, placebo-controlled trial. Abstract 2767. American College of Rheumatology 2013 Annual Meeting, San Diego, CA; 2013. *Arthritis Rheum* 2013;65(Suppl S10):S1182. Available at http://onlinelibrary.wiley.com/doi/10.1002/art.38216/abstract (last accessed 11 April 2016).
45. Kavanaugh A, Fleischmann RM, Emery P, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64–71.[PubMed]
46. Detert J, Bastian H, Listing J, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy alone for DMARD naïve patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844–850.[PubMed]
47. Hørslev-Petersen K, Hetland ML, Junker P, et al. Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA study: an investigator-initiated, randomized, double blind, parallel-group, placebo-controlled trial. *Ann Rheum Dis* 2014;73:654–661.[PubMed]
48. Bejarano V, Quinn M, Conaghan PG, et al; Yorkshire Early Arthritis Register Consortium. Effect of the early use of anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early RA. *Arthritis Rheum* 2008;59:1467–1474.[PubMed]
49. Takeuchi T, Yamanaka H, Ishiguro N, et al. Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. *Ann Rheum Dis* 2014;73:536–543.[PubMed]
50. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomized, double blind, parallel treatment trial. *Lancet* 2008;372:375–382.[PubMed]
51. Nam JL, Villeneuve E, Hensor EM, et al. A randomized controlled trial of etanercept and methotrexate to induce remission in early inflammatory arthritis: the EMPIRE trial. *Ann Rheum Dis* 2014;73:1027–1036.[PubMed]
52. Nam JL, Villeneuve E, Hensor EM, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double blind, randomized, controlled trial in new-onset, treatment naïve, rheumatoid arthritis (the IDEA study). *Ann Rheum Dis* 2014;73:75–85.[PubMed]
53. Leirisalo-Repo M, Kautiainen H, Laasonen L, et al; NEO-RACo Study Group. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomized, double-blind, placebo-controlled study. (the NEO-RACo Study). *Ann Rheum Dis* 2013;72:851–857.[PubMed]
54. St Clair EW, van der Heijde DM, Smolen JS, et al; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432–3443.[PubMed]
55. Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52:3381–3390.[PubMed]
56. Tak PP, Rigby WF, Rubbert-Roth A, et al; IMAGE Investigators. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. *Ann Rheum Dis* 2011;70:39–46.[PubMed]
57. Hoes JN, Jacobs JWG, Boers M, et al. EULAR evidence based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007;66:1560–1567.[PubMed]
58. Gøtzsche PC, Johansen HK. Meta-analysis of short-term low dose prednisolone versus placebo and non-steroidal anti-inflammatory drugs in rheumatoid arthritis. *BMJ* 1998;316:811–818.[PubMed]
59. Criswell L, Saag K, Sems KM. Moderate-term, low-dose corticosteroids for rheumatoid arthritis. In: The Cochrane Library, Issue 12, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 1998.
60. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. In: The Cochrane Library, Issue 12, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2005.
61. Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1010–1014.[PubMed]
62. Suponitskaia EV, Smirnov AV, Aleksandrova EN, et al. Effect of small-dose glucocorticoids on the course of early rheumatic arthritis. *Klin Med (Mosk)* 2004;82:39–42. [In Russian][PubMed]
63. Choy EH, Smith CM, Farewell V, et al; CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) Trial Group. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis* 2008;67:656–663.[PubMed]
64. Bakker MF, Jacobs JW, Welsing PM, et al; Utrecht Rheumatoid Arthritis Cohort Study Group. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012;156:329–339.[PubMed]
65. Montecucco C, Todoerti M, Sakellariou G, et al. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. *Arthritis Res Ther* 2012;14:R112.[PubMed]
66. Todoerti M, Scirè CA, Boffini N, et al. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. *Ann N Y Acad Sci* 2010;1193:139–145.[PubMed]
67. Fedorenko E, Lukina GV, Sigidin YA, et al. Remission as the main goal of treatment in early rheumatoid arthritis patients: comparative efficacy of four treatment regimens. *Ann Rheum Dis* 2011;70(Suppl 3):598.
68. Kirwan JR; Arthritis and Rheumatism Council Low-dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;333:142–146.[PubMed]
69. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;350:309–318.[PubMed]
70. Capell HA, Madhok R, Hunter JA, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. *Ann Rheum Dis* 2004;63:797–803.[PubMed]
71. Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 2005;52:3360–3370.[PubMed]
72. Wassenberg S, Rau R, Steinfeld P, et al; Low-Dose Prednisolone Therapy Study Group. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:3371–3380.[PubMed]
73. Hickling P, Jacoby RK, Kirwan JR, et al; Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. *Br J Rheumatol* 1998;37:930–936.[PubMed]
74. Buttgereit F, da Silva J, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002;61:718–722.[PubMed]
75. van Rensburg K. A guide to prescribing corticosteroids. *S Afr Pharm J* 2011;78:32–38.
76. Mager DE, Lin SX, Blum RA, et al. Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics. *J Clin Pharmacol* 2003;43:1216–1227.[PubMed]

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Disclaimer

GRADE **Evaluation of interventions for Rheumatoid arthritis: previously untreated early disease.**

Important outcomes	Symptom severity (clinical symptoms), Symptom severity (function), Symptom severity (joint damage)								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of methotrexate in combination with other csDMARDs versus methotrexate monotherapy in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)?									
3 (313) [32] [33] [34]	Symptom severity (joint damage)	Methotrexate plus other csDMARD therapy versus methotrexate monotherapy	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting and weak methods (including unclear randomisation and allocation concealment in some studies)
8 (1923) [32] [33] [34] [35] [36] [37] [38] [39]	Symptom severity (clinical symptoms)	Methotrexate plus other csDMARD therapy versus methotrexate monotherapy	4	–3	0	–1	0	Very low	Quality points deducted for weak methods (including incomplete reporting of results, differences in dose increases of methotrexate, unclear randomisation and loss to follow-up); directness point deducted for use of additional concurrent treatments in some trials
7 (1334) [32] [34] [35] [36] [37] [38] [39]	Symptom severity (function)	Methotrexate plus other csDMARD therapy versus methotrexate monotherapy	4	–3	0	–1	0	Very low	Quality points deducted for weak methods (including incomplete reporting of results, differences in dose increases of methotrexate, unclear randomisation and loss to follow-up); directness point deducted for use of additional concurrent treatments in some trials
What are the effects of bDMARDs in combination with methotrexate versus methotrexate monotherapy or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)?									
2 (1120) [45] [46]	Symptom severity (joint damage)	Adalimumab plus methotrexate versus methotrexate monotherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (at least 1326) [45] [46] [47]	Symptom severity (clinical symptoms)	Adalimumab plus methotrexate versus methotrexate monotherapy	4	–1	–1	0	0	Low	Quality point deducted for discontinuation of adalimumab and placebo interventions after 24 weeks in one trial; consistency point deducted for inconsistent results across different studies and at different time points
3 (at least 1326) [45] [46] [47]	Symptom severity (function)	Adalimumab plus methotrexate versus methotrexate monotherapy	4	–1	–1	0	0	Low	Quality point deducted for discontinuation of adalimumab and placebo interventions after 24 weeks in 1 trial; consistency point deducted for inconsistent results across different studies and at different time points
1 (unclear) [50]	Symptom severity (joint damage)	Etanercept plus methotrexate versus methotrexate monotherapy	4	–1	0	–1	0	Low	Quality point deducted for subgroup analysis with exact number in analysis unclear; directness point deducted for concomitant GCs

Important outcomes	Symptom severity (clinical symptoms), Symptom severity (function), Symptom severity (joint damage)								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (unclear) [50]	Symptom severity (clinical symptoms)	Etanercept plus methotrexate versus methotrexate monotherapy	4	–1	0	–1	0	Low	Quality point deducted for subgroup analysis with exact number in analysis unclear; directness point deducted for concomitant GCs
1 (unclear) [50]	Symptom severity (function)	Etanercept plus methotrexate versus methotrexate monotherapy	4	–1	0	–1	0	Low	Quality point deducted for subgroup analysis with exact number in analysis unclear; directness point deducted for concomitant GCs
1 (112) [52]	Symptom severity (joint damage)	Infliximab plus methotrexate versus methotrexate plus glucocorticoid	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (112) [52]	Symptom severity (clinical symptoms)	Infliximab plus methotrexate versus methotrexate plus glucocorticoid	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (112) [52]	Symptom severity (function)	Infliximab plus methotrexate versus methotrexate plus glucocorticoid	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of glucocorticoids in combination with methotrexate or with other csDMARDs versus methotrexate or other csDMARDs in people with rheumatoid arthritis who have not previously received any DMARD treatment (first-line treatment)?									
5 (unclear) [55] [62] [63] [64] [65]	Symptom severity (joint damage)	Glucocorticoids plus methotrexate (with or without other csDMARDs) versus methotrexate (with or without other csDMARDs)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (unclear) [55] [63] [64] [65] [66] [67]	Symptom severity (clinical symptoms)	Glucocorticoids plus methotrexate (with or without other csDMARDs) versus methotrexate (with or without other csDMARDs)	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and one RCT reported from abstract only
2 (unclear) [55] [64]	Symptom severity (function)	Glucocorticoids plus methotrexate (with or without other csDMARDs) versus methotrexate (with or without other csDMARDs)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (at least 622) [68] [69] [70] [71] [72]	Symptom severity (joint damage)	Glucocorticoids plus other csDMARDS (or combination of csDMARDs) versus other csDMARDS (or combination of csDMARDs)	4	–2	0	0	0	Low	Quality points deducted for lack of blinding in one RCT, inconsistencies in reporting, and results provided by the two x-ray readers differing considerably in one RCT
5 (unclear; at least 632) [68] [69] [70] [71] [72]	Symptom severity (clinical symptoms)	Glucocorticoids plus other csDMARDS (or combination of csDMARDs) versus other csDMARDS (or combination of csDMARDs)	4	–1	–1	0	0	Low	Quality point deducted for lack of blinding in one RCT; consistency point deducted for difference in results between studies and over time
4 (unclear) [68] [69] [70] [71]	Symptom severity (function)	Glucocorticoids plus other csDMARDS (or combination of csDMARDs) versus other csDMARDS (or combination of csDMARDs)	4	–1	0	0	0	Moderate	Quality point deducted for lack of blinding in one RCT

Important outcomes	Symptom severity (clinical symptoms), Symptom severity (function), Symptom severity (joint damage)								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.									